(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 223 420**
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 86308087.5

(22) Date of filing: 17.10.86

(51) Int. Cl.⁴: C07D 471/04 , C07D 495/14 , A61K 31/47 , //(C07D471/04,235:00,221:00),(-C07D495/04,333:00,235:00,221-:00)

(30) Priority: 18.10.85 JP 234357/85
23.05.86 JP 119681/86

(43) Date of publication of application:
27.05.87 Bulletin 87/22

(84) Designated Contracting States:
BE CH DE ES FR IT LI NL SE

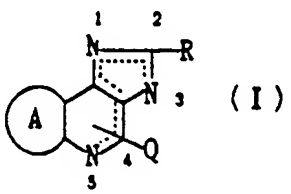
(71) Applicant: SHIONOGI & CO., LTD.
12, Dosho-machi 3-chome Higashi-ku
Osaka 541(JP)

(72) Inventor: Takada, Susumu
4-6-78, Midoridai
Kawanishi-shi Hyogo(JP)
Inventor: Fujishita, Toshio
A6-302, 334-01, Kunimori-cho
Neyagawa-shi Osaka(JP)
Inventor: Sasatani, Takashi
2182-9, Mise-cho
Kashihara-shi Nara(JP)
Inventor: Matsushita, Akira
2-3-22, Fukaeminamimachi Higashinada-ku
Kobe-shi Hyogo(JP)
Inventor: Eigyo, Masami
2-10-7, Shikanodainishi
Ikoma-shi Nara(JP)

(74) Representative: Bizley, Richard Edward et al
BOULT, WADE & TENNANT 27 Furnival Street
London EC4A 1PQ(GB)

(54) **Condensed imidazopyridine derivatives.**

EP 0 223 420 A1



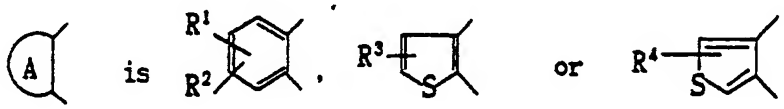
(I)

(57) (wherein R is phenyl optionally substituted by one or two members selected from the group consisting of

trifluoromethyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 alkylthio, nitro, amino C_1-C_5 alkanoylamino and C_1-C5 alkoxycarbonyl or

5-or 6-membered heterocyclic group optionally substituted by one or two members selected from the group consisting of halogen, C_1-C_5 alkyl and C_1-C_5 alkoxy,

Q is hydrogen, C_1-C_5 alkyl, C_1-C_{10} acyl, C_1-C_5 alkylsulfonyl or C_5-C_{10} arylsulfonyl,



R^1, R^2, R^3, and R^4 each is hydrogen, halogen C_1-C_5 alkyl, C_1-C_5 alkoxy or C_1-C_5 haloalkyl,

Q is present on the nitrogen atom of the 1,3 or 5-position and the dotted line indicates the presence of three double bonds at the position of 2, 3; 3a, 3b; 4, 5 / 1, 3b; 2, 3; 3a, 4 / or 1, 2; 3a, 3b; 4, 5) or its salt, being useful as psychostimulants or anxiolytics, is provided.

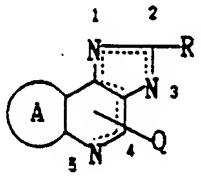
Condensed Imidazopyridine Derivatives

The present invention relates to condensed imidazopyridine derivatives. More particularly, this invention is directed to condensed imidazopyridine derivatives which have been found to be particularly effective in the treatment of depression or anxiety, to their preparation, to their use and to pharmaceutical and veterinary formulations containing the compounds.

USSR pat. No. 509,588 discloses that 1H-2-oxo-3-phenyl-7-methyl-imidazo[4,5-c]quinoline is useful as a synthetic intermediate to biologically active materials. Abbasi et al, [Monatsh. Chem., 111, 963 (1980)] disclose 3-hydroxy-2-hydroxymethyl-8-methoxy-9-nitro-4-styryl-2H-imidazo[4,5-c]quinoline and its analogs as synthetic intermediates to biologically active materials. Further European Pat. Appln. No. 145,340 describes 2-hydroxyalkyl-1H-imidazo[4,5-c]quinolines useful as bronchodilators or antiviral agents.

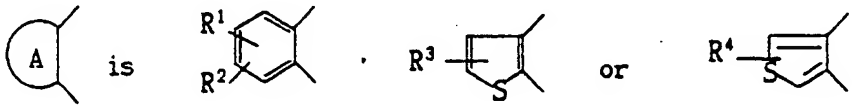
The condensed imidazopyridine derivatives of the present invention are those having a 2-position phenyl optionally substituted by one or two members selected from trifluoromethyl, C_1-C_5 alkyl, C1-C5 alkoxy, C_1-C_5 alkylthio, nitro, amino, C_1-C_5 alkanoylamino and C_1-C_5 alkoxycarbonyl, or a 5-or 6-membered heterocyclic group optionally substituted by one or two members selected from halogen, C_1-C_5 alkyl and C_1-C_5 alkoxy.

According to the present invention there is provided a condensed imidazopyridine derivative of the formula:



(I)

wherein R is phenyl optionally substituted by one or two of trifluoromethyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 alkylthio, nitro, amino, C_1-C_5 alkanoylamino and C_1-C_5 alkoxycarbonyl or a 5-or 6-membered heterocyclic group optionally substituted by one or two of halogen, C_1-C_5 alkyl and C_1-C_5 alkoxy; Q is hydrogen, C_1-C_5 alkyl, C_1-C_{10} acyl, C_1-C_5 alkylsulfonyl or C_6-C_{10} arylsulfonyl;

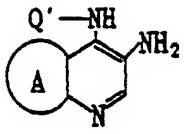


R^1, R^2, R^3 and R^4 are each independently hydrogen, halogen, C_1-C_5 alkyl, c_1-c_5 alkoxy or c_1-c_5 haloalkyl; Q is present on the nitrogen atom at the 1, 3 or 5-position; and the dotted line indicates the presence of three double bonds at the position of 2, 3; 3a, 3b; 4, 5 / 1, 3b; 2, 3; 3a, 4 / or 1, 2; 3a, 3b; 4, 5). The invention further relates to compounds of formula I which are acid addition salts thereof.

The compounds of the present invention have an excellent psychotropic activity such as psychostimulant or anxiolytic activity with no undesirable side effects. Accordingly, the compound may be used in a psychotropic formulation comprising as an active ingredient 0 1 to 95% by weight of a compound of the formula (I) associated with at least one carrier, diluent or excipient therefor.

The compounds of the invention may be used in the treatment of a a patient suffering from depression or anxiety by the administration to the patient of a pharmacologically effective amount of a compound of the formula (I).

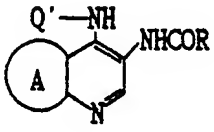
The invention further provides a process for preparing a compound of the formula (I) which comprises reacting a compound of the formula:



(II)

wherein Q' is hydrogen or C_1-C_5 alkyl, and

is as defined above with an acylating agent to give a compound of the formula:



(III)

wherein

, Q' and R each is as defined above and cyclizing the compound (III) and then Q' is hydrogen, applying the cyclized product to alkylation, acylation or sulfonylation, if necessary.

The term "C_1-C_5 alkyl" herein employed may include a straight or branched saturated aliphatic hydrocarbon radical such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl or 1-methylisobutyl.

The term "C_1-C_5 alkoxy" may include an alkoxy group containing a c_1-C_5 alkyl moiety such as methoxy, ethoxy, propoxy, isopropoxy, butoxy and pentyloxy.

The term "C_1-C_5 alkylthio" may include an alkylthio group containing a c_1-c_5 alkyl moiety such as methylthio, ethylthio, propylthio, butylthio isobutylthio and neopentylthio.

The term "C_1-C_5 alkanoylamino" includes formylamino, acetylamino, propionylamino, butyrylamino, valerylamino and isovalerylamino.

The term "C_1-C_5 alkoxycarbonyl" includes methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and pentyloxycarbonyl.

The term "5-or 6-membered heterocyclic group" includes isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, thiadiazolyl, oxadiazolyl, thienyl, furyl and pyridyl.

The term "C_6-C_{10} acyl" includes C_1-C_5 alkanoyl such as formyl, acetyl, propionyl, butyryl, valeryl or isovaleryl and C_7-C_{11} aroyl such as benzoyl, toluoyl or propylbenzoyl.

The term "C_1-C_5 alkylsulfonyl" includes methylsulfonyl, ethylsulfonyl, propylsulfonyl, isobutylsulfonyl and pentylsulfonyl.

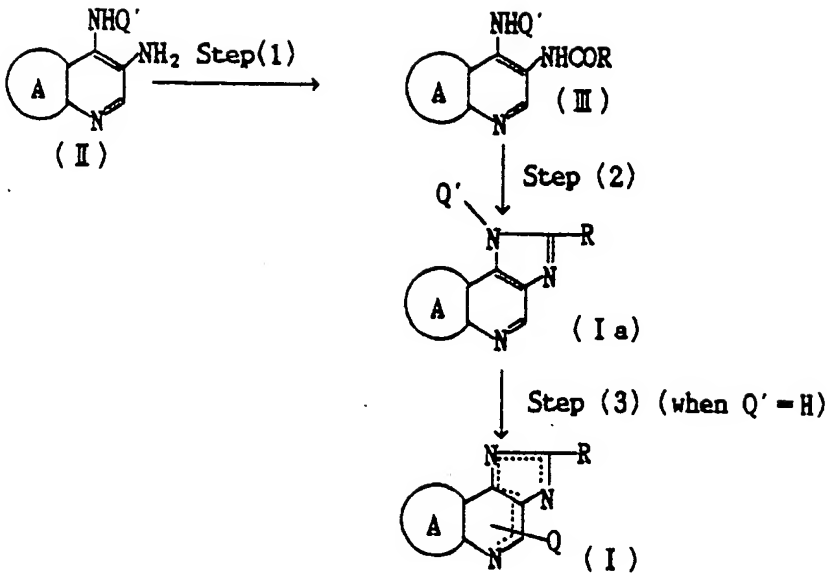
The term "C_5-C_{10} arylsulfonyl" includes phenylsulfonyl, tolylsulfonyl, xylylsulfonyl and naphthylsulfonyl.

The term " C_1-C_5 haloalkyl" includes fluoromethyl, chloroethyl, bromopropyl, iodobutyl and trifluoromethyl.

The term "halogen" includes fluorine, chlorine bromine and iodine.

The process for preparing the compound (I) may be shown by the scheme as follows:

SCHEME



(wherein Q' is hydrogen or C_1-C_5 alkyl, and  , Q and R are as defined above).

Step (1)

The amide (III) can be prepared by reacting the diamine (II) with an acylating reagent. The reaction may be performed at a comparatively lower temperature (e.g. -10 to 5°C) generally in an appropriate solvent, using an acylating agent containing a necessary acyl group. The solvent includes illustratively dimethylformamide, acetonitrile, chloroform, hexamethylphosphoramide, ether, tetrahydrofuran or mixtures thereof. The

acylating reagent refers to an acid halogenide such as acid chloride or acid bromide; a mixed acid anhydride; a mixture of carboxylic acid with thionyl chloride; a mixture of carboxylic acid with a condensing agent such as DCC or polyphosphoric acid.

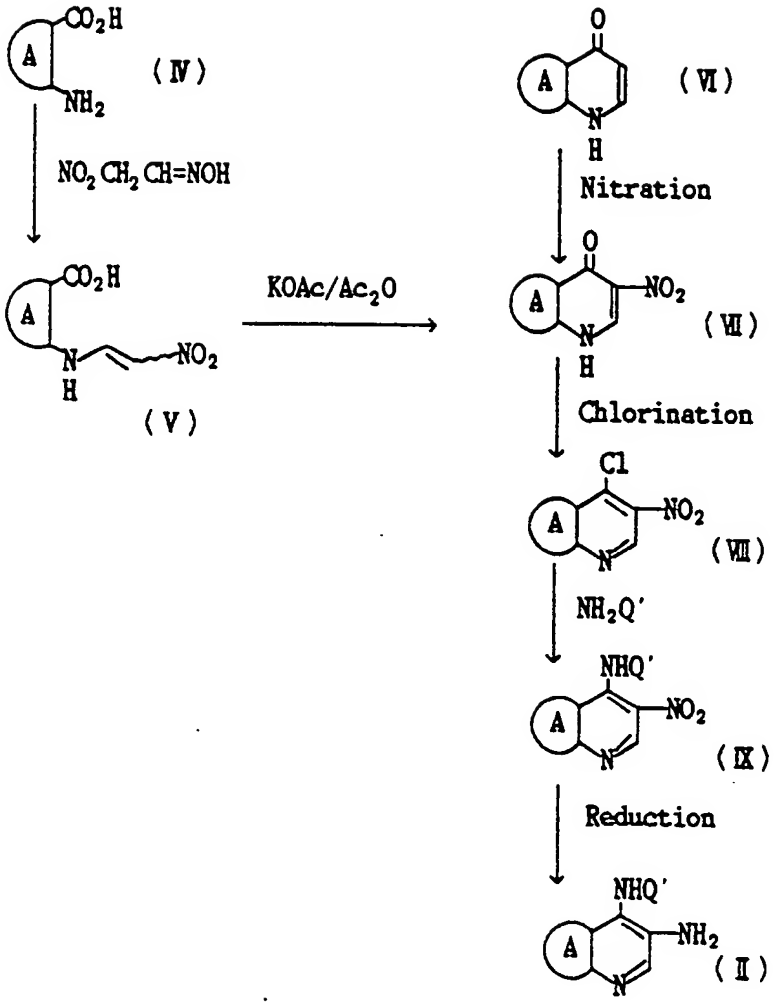
Step (2)

The compound (Ia) can be prepared by heating the amide (III) in a solvent at a temperature from about 50°C to 250°C, preferably 100°C to 250°C in the presence or absence of cyclizing agent such as polyphosphoric acid, polyphosphoric ester, sulfuric acid, acetic acid or phosphorus pentoxide. The solvent includes illustratively hexamethylphosphoramide, diphenyl ether, glycerin triethyl ether, butyl ether, isoamyl ether, diethylene glycol, triethylene glycol or Dowtherm A (Dow Chemical Co.).

Step (3)

As necessary, the compound (Ia) (Q' = Hydrogen) may be subjected to alkylation, acylation or sulfonylation. The reaction may be performed with an alkylating, acylating or sulfonylating agent in an appropriate solvent in the presence of a base such as alkali metal hydride. (e.g. sodium hydride, potassium hydride) or alkali metal alkoxide (e.g. sodium methoxide, potassium ethoxide, sodium isopropoxide) at a temperature of 30 to 120°C. The alkylating agent includes alkyl halide such as methyl iodide, ethyl bromide, propyl chloride or butyl iodide and dialkyl sulfate such as dimethyl sulfate or diethyl sulfate. The acylating agent includes acyl halide such as acetyl chloride, propionyl bromide, butyryl chloride or benzoyl chloride and acid anhydride such as acetic anhydride or propionic anhydride. The sulfonylating agent includes mesyl chloride, butylsulfonyl chloride and tosyl chloride. As solvents there are exemplified tetrahydrofuran, dioxane, diglyme, dimethylformamide, chloroform and ethanol.

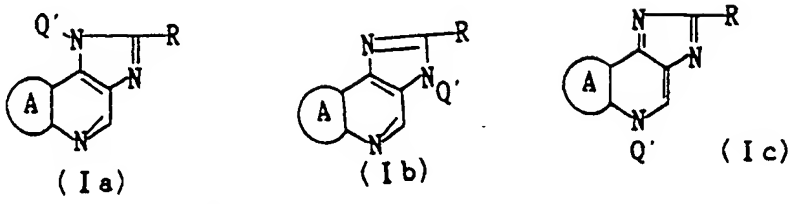
The diamine (II) usable as a starting material can be prepared, as shown below, in accordance with the methods of G. B. Bachman et al., J. Am. Chem. Soc., 69, 365 (1947) and A. R. Surrey et al., J. Am. Chem. Soc., 73, 2413 (1951).



(wherein Ac is acetyl;

and Q' are as defined above.)

The compound (I) includes the following three compounds (I^a, I^b and I^c):



(wherein  , Q' and R are as defined above).

The compound (I) can be converted into its physiologically acceptable acid addition salts. Such acids illustratively include an inorganic acid such as hydrochloric acid, sulfuric acid, phosphoric acid or nitric acid and an organic acid such as acetic acid, maleic acid, malic acid, citric acid, lactic acid, succinic acid or methanesulfonic acid.

The invention further relates to a pharmaceutical or veterinary formulation comprising a compound of formula (I) formulated for pharmaceutical or veterinary use, respectively. The formulation may be in unit dosage form and/or may further comprise a pharmaceutically or veterinarily acceptable carrier, diluent or excipient.

The compound of formula (I) and its salts may be of general use in the treatment of disease. The invention includes the use of the compound of formula (I) and its salts in the manufacture of a medicament for the treatment of anxiety or depression.

The compounds (I) or acceptable acid addition salts thereof have a high affinity to benzodiazepine receptors, and they are useful as psychotropic agents such as psychostimulants or anxiolytics.

The compounds (I) can be administered orally or parenterally to human beings or other animals. They can be formulated as tablets, capsules, pills, granules, injections, suppositories, and syrups As acceptable carriers, diluents or excipients there are exemplified lactose, sucrose, wheat starch, potato starch, magnesium stearate, gelatin, methyl cellulose, agar, water, and the like. As necessary, appropriate stabilizers, emulsifiers, spreaders, buffers and other adjuvants can be added. Appropriate daily dosage of the compound (I) is 0.1 to 500 mg in oral route and 0.1 to 300 mg in injection.

The present invention may be explained in more detail by the following non-limiting Examples, Referential Examples and Formulations.

The abbreviations used in Examples, Referential Examples and Tables have the following meanings.

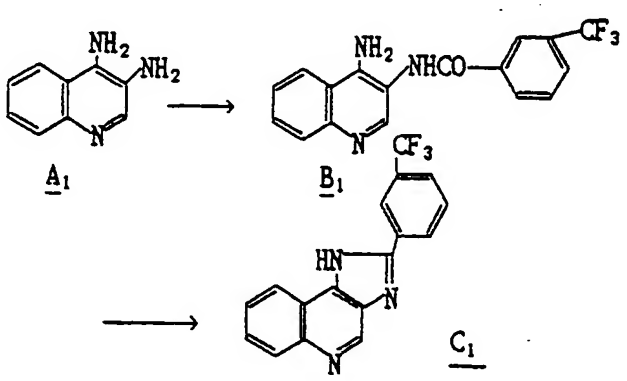
HMPA : Hexamethylphosphoramide
Me : Methyl
Et : Ethyl
PPA : Polyphosphoric acid
MeCN : Acetonitrile
MeOH : Methanol
EtOH : Ethanol
Et_2O : Ether
AcOEt : Ethyl acetate
AcOH : Acetic acid
DMF : Dimethylformamide
(d) : Decomposition

When Q is hydrogen, the compound (Ia) and (Ib) being a tautomer of each other will be named conveniently as said formula (Ia).

For example, 2-(3-trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline C, (Example 1) may be also named as 2-(3-trifluoromethylphenyl)-3H-imidazo[4,5-c[quinoline.

Example 1

2-(3-Trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline C,

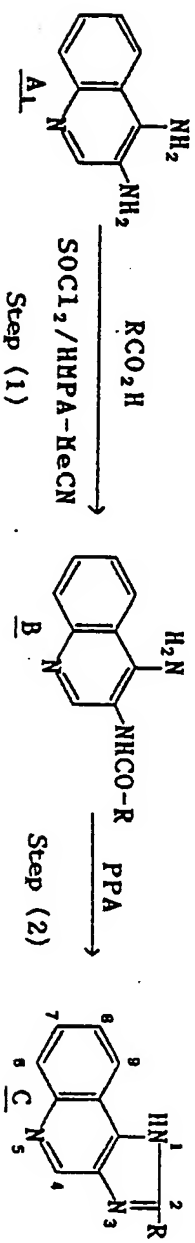


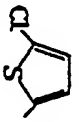
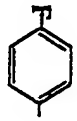
To a solution of 500 mg of 3-trifluoromethylbenzoic acid in 6 ml of anhydrous hexamethylphosphoramide (HMPA) and 0.6 ml of anhydrous acetonitrile is added dropwise 305 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at the same temperature for 30 minutes, 380 mg of 3,4-diaminoquinoline is added and stirred at 0 -5°C for 3 hours. The mixture is diluted with ice-water and neutralized with saturated aqueous sodium bicarbonate. The resulting crystals are filtered, washed with water, and dried to give 780 mg of 4-amino-3-(3-trifluoromethylbenzoylamino)quinoline B$_1$ as a crude product. It is suspended in 15 g of polyphosphoric acid and heated at 120°C for 4 hours with stirring. The mixture is poured into ice-water and neutralized with 1N soium hydroxide. The resulting solid is filtered, washed with water and dried. It is chromatographed on silica gel with chloroform -methanol (10:1 v/v) as eluent, yielding 350 mg (47%) of C$_1$ as colorless crystals.
m.p. 254 -256°C (from ethyl acetate)
Anal.Calcd.(%)(for $C_{17}H_{10}N_3F_3$)
: C, 65.18; H, 3.22; N, 13.41; F, 18.19.
Found (%) : C, 64.74; H, 3.54; N, 13.20; F, 18.30.

Example 2-3

According to the method illustrated by Example 1, the compounds C$_2$ and C$_3$ are prepared under the conditions shown in Table 1. Table 3 shows the physical properties of these compounds.

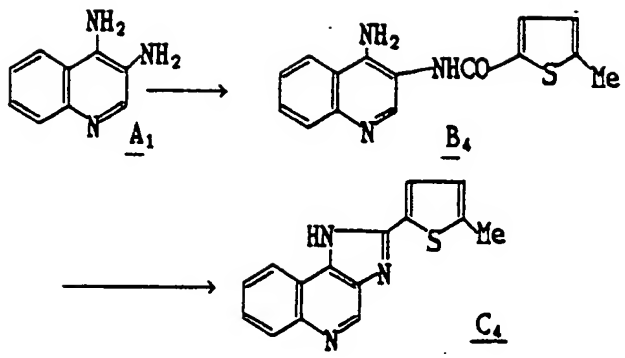
Table 1



Ex. No.	R	Step (1)				Step (2)					
		RCO_2H (mg)	$SOCl_2$ (mg)	HMPA–MeCN (ml) (ml)	Compd. A_1 (mg)	Reaction Time (hr)	PPA (g)	Temp. (°C)	Reaction Time (hr)	Compd. C Yield (mg)	Compd. C Yield (%) from A_1	Compd. No.
2		420	305	6 0.6	380	3.5	15	120	7.5	365	54	C_2
3		370	305	6 0.6	380	3.5	12	135	4	480	76	C_3

Example 4

2-(5-Methylthien-2-yl)-1H-imidazo[4,5-c]quinoline C_4



To a solution of 555 mg of 5-methylthiophene-2-carboxylic acid in 9 ml of anhydrous hexamethylphosphoramide and 0.9 ml of anhydrous acetonitrile is added dropwise 455 mg of thionyl chloride at -5 - 0°C under nitrogen. After stirring at the same temperature for 30 minutes, 570 mg of 3,4-diaminoquinoline is added and stirred at 0 -5°C for 4 hours. THe same work-up as described in Example 1 gives 900 mg of 4-amino-3-(5-methylthien-2-ylcarbonylamino)quinoline $\underline{B_4}$ as a white solid. It is suspended in 15 g of polyphosphate ester and heated at 125°C with stirring for 3 hours. The mixture is diluted with ice-water and neutralized with 1N sodium hydroxide and extracted with ethyl acetate. The extract is washed with water and saturated sodium chloride, dried over magnesium sulfate, and evaporated. The residue is chromatographed on silica gel with chloroform -methanol (10:1 v/v) as eluent to give 456 mg (48%) of $\underline{C_4}$ as pale yellow crystals.

m.p. 293 -295°C (dec.) (from ethanol)

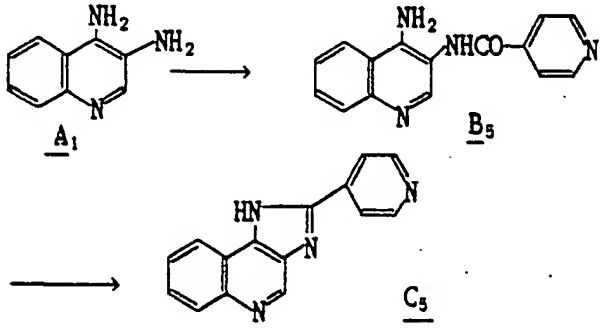
Anal. Calcd. (%) (for $C_{15}H_{11}N_3S$)

: C, 67.90; H, 4.18; N, 15.84; S, 12.08.

Found (%) : C, 68.16; H, 4.25; N, 15.76; S, 11.63.

Example 5

2-(Pyridin-4-yl)-1H-imidazo[4,5-c]quinoline C_5

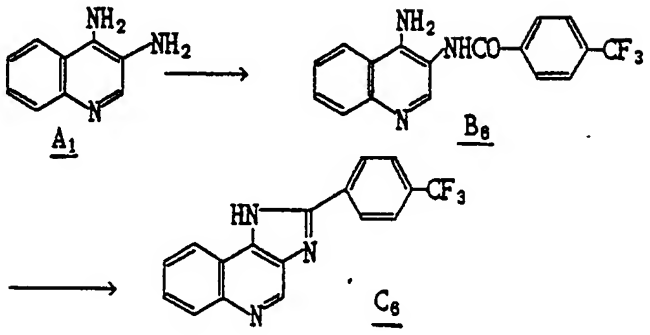


To a solution of 325 mg of isonicotinic acid in 8 ml of anhydrous hexamethylphosphoramide and 0.8 ml of anhydrous acetonitrile is added dropwise 305 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring for 45 minutes, 380 mg of 3,4-diaminoquinoline $\underline{A_1}$ is added and the mixture is stirred at 0°C for 4.5 hours. The same work-up as described in Example 1 gives 560 mg of crude crystals of $\underline{B_5}$. It is dissolved in 10 ml of acetic acid and refluxed for 4 hours. The mixture is concentrated under reduced pressure and mixed with ice-water and neutralized with saturated sodium bicarbonate. The resulting crystals are filtered

and dried to yield 510 mg (87%) of C_5 as white crystals.
m.p. 270 -272°C(from ethyl acetate -methanol)
Anal. Calcd.(%) (for $C_{15}H_{10}N_4$)
: C, 73.16; H, 4.09; N, 22.75.
Found (%) : C, 72.79; H, 4.20; N, 22.37.

Example 6

2-(4-Trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline C_6

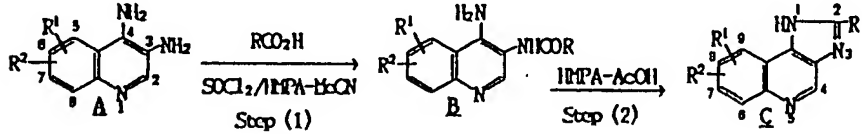


To a solution of 395 mg of 4-trifluoromethylbenzoic acid in 5 ml of anhydrous hexamethylphosphoramide and 0.5 ml of anhydrous acetnoitrile is added dropwise 240 mg of thionyl chloride at -5 - 0°C under nitrogen. After stirring at the same temperature for 30 minutes, 300 mg of 3,4-diaminoquinoline A_1 is added and stirred at 0 -5°C for 4 hours. The same work-up as described in Example 1 gives 605 mg of the crude crystals of B_6. It is suspended in 10 ml of hexamethylphosphoramide and 2.5 ml of acetic acid, and stirred at 155°C for 15 minutes under nitrogen. The cooled mixture is diluted with water and neutralized with saturated aqueous sodium bicarbonate. The resulting solid is chromatographed on silica gel with chloroform -methanol (10:1 v/v) as eluent to give 440 mg (75%) of C_6 as white crystals.
m.p.: >340°C (from ethanol)
Anal.Calcd. (%) (for $C_{17}H_{10}N_3F_3$)
: C, 65.18; H, 3.22; N, 13.41; F, 18.19.
Found (%) : C, 64.95; H, 3.44; N, 13.24; F, 18.10

Example 7-93

According to the method illustrated by Example 6, Compounds C_7 C_{93} are prepared under the conditions shown in Table 2. Table 3 shows the physical properties of these compounds.

Table 2 (1)



Ex. No.	R	Step (1)							Step (2)				Compd. C		
		RCO_2H (mg)	$SOCl_2$ (mg)	HMPA (ml)	MeCN (ml)	R^1	R^2	Compd. (mg)	Reaction time (hr)	HMPA (ml)	AcOH (ml)	Temp. (°C)	Reaction Time (min)	Yield (mg)	Yield (%) from Compd. A	Compd. No.
7		670	710	12	1.2	H	H	760	3.5	20	5	155	100	875	73	C_7
8		520	305	6	0.6	H	H	380	3.5	12	3	150	35	560	73	C_8
9		420	305	6	0.6	H	H	380	4.5	12	3	155	30	390	57	C_9
10		325	305	6	0.6	H	H	380	4.5	2	4	140	120	315	53	C_{10}
11		335	305	6	0.6	H	H	380	4.5	10	2.5	150	30	365	61	C_{11}
12		295	305	6	0.6	H	H	380	4.5	2	4	140	120	210	37	C_{12}
13		315	240	5	0.5	H	H	300	4.5	8	2	150	30	230	44	C_{13}

Table 2 (2)

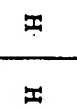
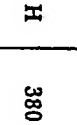
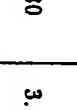
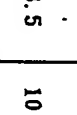
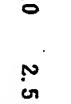
14		320	305	6	0.6	H	H	380	3.5	10	2.5	145	15	430	13	C_{14}
15		280	200	5	0.5	6-Cl	H	300	4.5	8	2	150	60	270	54	C_{15}
16		240	200	5	0.5	6-Cl	H	300	4.5	8	2	155	30	275	60	C_{16}
17		295	305	6	0.6	H	H	380	4.5	10	2.5	150	30	320	60	C_{17}
18		350	240	5	0.5	H	H	300	4.5	8	2	150	30	340	62	C_{18}
19		370	240	5	0.5	H	H	300	4.5	10	2.5	150	15	375	66	C_{19}
20		290	240	5	0.5	H	H	300	4.5	8	2	165	15	330	67	C_{20}
21		290	240	5	0.5	H	H	300	4.5	4	4	150	90	350	71	C_{21}
22		325	240	5	0.5	H	H	300	4.5	8	2	155	45	310	59	C_{22}
23		330	240	5	0.5	H	H	300	4.5	8	2	165	30	380	71	C_{23}
24		315	240	5	0.5	H	H	300	4.5	12	4	165	60	370	71	C_{24}

Table 2 (3)

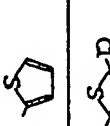
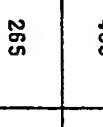
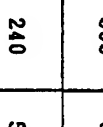
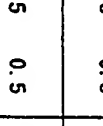
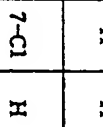
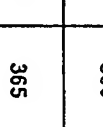
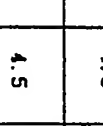
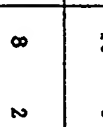
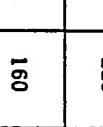
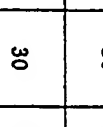
25		380	305	6	0.6	H	H	380	4.5	10	2.5	155	10	350	55	C_{11}
26		375	240	5	0.5	H	H	300	4.5	12	3	155	30	255	45	C_{11}
27		425	305	6	0.5	H	H	380	4.5	8	2	155	10	520	77	C_{11}
28		380	240	5	0.5	H	H	300	3.5	8	2	165	30	280	49	C_{11}
29		380	240	5	0.5	H	H	300	3.5	8	2	165	20	390	68	C_{11}
30		350	240	5	0.5	H	H	300	5.5	10	2.5	165	60	460	84	C_{11}
31		330	240	5	0.5	H	H	300	4.5	4	4	145	45	480	91	C_{11}
32		330	240	5	0.5	H	H	300	4.5	4	4	140	30	470	89	C_{11}
33		330	240	5	0.5	H	H	300	3.5	6	4	155	30	430	81	C_{11}
34		465	305	6	0.6	H	H	380	4.5	10	0	225	30	565	79	C_{11}
35		265	240	5	0.5	7-Cl	H	365	4.5	8	2	160	30	380	71	C_{11}

Table 2 (4)

36		290	240	5	0.5	7-Cl	H	365	4.5	8	2	160	15	385	69	C$_{33}$
37		375	305	6	0.5	H	H	380	4.5	10	2.5	160	45	540	85	C$_{37}$
38		295	240	5	0.5	7-Cl	H	365	4.5	8	2	165	40	400	71	C$_{33}$
39		295	240	5	0.5	7-Cl	H	365	4.5	8	2	170	10	380	67	C$_{33}$
40		290	240	5	0.5	6-F	H	330	4.5	8	2	165	10	425	81	C$_{33}$
41		295	240	5	0.5	6-F	H	330	4.5	8	2	160	15	390	74	C$_{33}$
42		206	181	4	0.4	7-Me	H	250	4	5.7	1.4	180	30	323	83	C$_{33}$
43		228	181	4	0.4	7-Me	H	250	5	6	1.5	180	60	325	81	C$_{33}$
44		214	192	5	0.5	6-Cl	7-Cl	343	2.5	8	2	170	40	314	65	C$_{33}$
45		1770	1250	20	2	H	H	2000	3	36	9	180	40	2940	93.6	C$_{33}$
46		274	220	4	0.4	H	H	280	4	6	1.5	180	30	338	73	C$_{33}$

Table 2 (5)

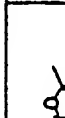
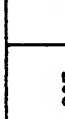
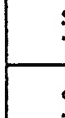
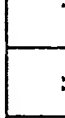
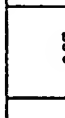
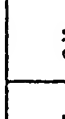
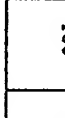
47		245	198	4	0.4	7-F	H	280	4	5	1.2	180	35	309	71	C$_{17}$
48		221	198	4	0.4	7-F	H	280	4	5	1.2	180	30	311	75	C$_{18}$
49		221	198	4	0.4	6-F	H	280	3	5	1.2	180	30	332	80	C$_{18}$
50		177	152	3.2	0.3	7-MeO	H	230	3	4	1	180	25	245	60	C$_{18}$
51		226	203	4	0.4	7-Me	H	280	4.5	4.8	1.2	180	25	319	76	C$_{19}$
52		210	188	4	0.4	6-Cl	H	290	3.5	5	1.2	180	35	265	62	C$_{18}$
53		192	171	4	0.4	6-F	7-Cl	290	4	5	1.2	180	40	364	89	C$_{18}$
54		210	188	4	0.4	7-Cl	H	290	4	4.8	1.2	180	30	281	67	C$_{18}$
55		184	166	4	0.4	7-CF$_3$	H	300	3	5	1.2	180	35	343	83	C$_{18}$
56		216	214	5	0.5	5-Cl	7-Cl	290	3	8	2	160	40	316	66	C$_{18}$
57		229	205	4	0.4	8-F	H	290	4.5	4	1	180	30	334	77	C$_{19}$

Table 2 (6)

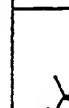
58		249	250	4 0.4	H	H	318	4	6 1.5	180	20	382	C,,
59		193	194	4 0.4	7-Cl	H	300	3.5	4 1	180	15	307	C,,
60		210	211	4 0.4	7-F	H	300	3	4 1	180	20	321	C,,
61		280	250	4.6 0.5	H	H	318	3.5	5.6 1.4	180	15	326	C,,
62		198	177	4 0.4	7-F	H	250	3	4.5 1.1	180	20	268	C,,
63		244	197	4 0.4	H	H	250	4	5 1.2	180	30	317	C,,
64		220	177	4 0.4	7-F	H	250	5	4.8 1.2	180	20	275	C,,
65		221	198	4 0.4	6-F	H	280	3.5	5.2 1.3	185	25	378	C,,
66		203	182	4 0.4	7-Cl	H	280	5	4.8 1.2	185	20	291	C,,
67		229	181	4 0.4	H	H	230	3.5	5 1.2	180	15	303	C,,
68		229	181	4 0.4	H	H	230	3.5	5 1.2	180	25	318	C,,

Table 2 (7)

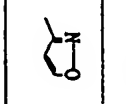
69		223	197	4	0.4	H	H	250	4	4.4	1.1	180	40	244	61	C_{11}
70		225	197	4	0.4	H	H	250	4.5	4.8	1.2	180	35	298	77	C_{11}
71		336	268	4	0.4	H	H	340	5	5	1.2	180	30	457	82	C_{11}
72		298	238	4	0.4	H	H	300	4	4	1	180	25	318	65	C_{11}
73		303	268	4	0.4	H	H	340	6	4	1	180	30	339	65	C_{11}
74		303	268	4	0.4	H	H	340	4	4	1	180	40	360	67	C_{11}
75		330	305	6	0.6	H	H	380	4.5	14	3.5	175	60	310	52	C_{11}
76		330	305	6	0.6	H	H	380	4.5	6	1	150	30	430	72	C_{11}
77		670	610	10	1	H	H	760	4.5	12	3	160	30	850	71	C_{11}
78		303	268	4	0.4	H	H	340	4	4	1	180	40	360	67	C_{11}
79		193	194	4	0.4	8-Cl	H	300	3	4	1	180	20	293	72	C_{11}

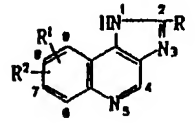
Table 2 (8)

80		246	4 0.4	8-F	H	350	3	4 1	180	25	303	60	C_{11}
81		562	7 0.7	6-F	H	800	5	8 2	180	25	862	75.4	C_{11}
82		244	4 0.4	6-OMe	H	370	4	5 1.2	180	30	403	77.4	C_{11}
83		497	7 0.7	7-F	H	708	5	0 9	118	60	679	808	C_{11}
84		249	4 0.4	8-F	H	354	4	4.8 1.2	180	30	395	77.8	C_{11}
85		249	4 0.4	7-Me	H	354	4	4 1	180	35	390	78.0	C_{11}
86		199	4 0.4	7-CF_3	H	360	3.5	4 .1	180	30	376	78.0	C_{11}
87		374	5 0.5	5-F	H	531	3.5	4 1	180	30	367	48.2	C_{11}
88		282	4 0.4	5-F	H	354	4	4.8 1.2	180	50	432	80.3	C_{11}
89		200	4 0.4	8-F	H	250	4	5.6 1.4	180	35	312	87.6	C_{11}
90		245	4 0.5	5-Cl	H	312	3.0	7 2	160	40	312	72	C_{11}

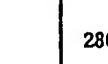
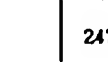
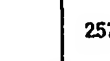
Table 2 (9)

91	92	93
		
278	309	315
344	331	283
4 0.5	4 0.5	5 0.5
5-Cl	5-Cl	5-?
H	H	H
313	311	400
2.3	3.0	4
6 2	6 2	4 1
160	163	180
40	45	40
268	346	303
58	72	50
C,,	C,,	C,,

Table 3 (1)



C

Compd. No.	R¹	R²	R	m. p. (°C)	Appearance	Solvent for Crystallo.	Molecular Formula	Elementary Analysis (%)				Up : Calcd. Down : Found
								C	H	N	S	
C₆	H	H		296-298	light yellow	EtOH	$C_{14}H_9N_3SCl$	58.85 58.86	2.82 3.22	14.71 14.40	11.22 11.22	Cl 12.41 Cl 12.34
C₈	H	H		300-301	colorless	EtOH	$C_{14}H_{10}N_3F$	72.99 72.90	3.83 4.13	15.96 15.75		F 7.22 F 7.17
C₇	H	H		304-305	colorless	EtOH	$C_{14}H_9N_3S$	66.91 66.94	3.61 3.55	16.72 16.61	12.76 12.52	
C₉	H	H		225-227	colorless	AcOEt-n-hexane	$C_{14}H_7N_3SCl_2$	52.52 52.23	2.20 2.58	13.12 13.00	10.01 9.95	Cl 22.14 Cl 22.05
C₅	H	H		286-288	colorless	EtOH	$C_{14}H_9N_3SCl$	58.85 58.93	2.82 2.88	14.71 14.62	11.22 11.44	Cl 12.41 Cl 12.45
C₁₀	H	H		247-249	colorless	EtOH	$C_{14}H_{10}N_4$	73.16 73.34	4.09 4.43	22.75 22.54		
C₁₁	H	H		280-282	colorless	EtOH-AcOEt	$C_{14}H_9N_3S$	66.91 66.64	3.61 3.66	16.72 16.49	12.76 12.60	
C₁₂	H	H		257-258	colorless	AcOEt	$C_{14}H_9N_3O$	71.48 71.46	3.86 3.92	17.86 17.79		
C₁₃	H	H		292-293	colorless	MeOH-AcOEt	$C_{17}H_{13}N_3O$	74.17 73.80	4.76 4.90	15.26 14.84		

0 223 420

22

Table 3 (2)

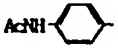
C_{11}	H	H		298-300	color-less	EtOH	$C_{15}H_{11}N_3$	78.35 78.06	4.52 4.47	17.13 17.04		
C_{11}	8-Cl	H		315-316	color-less	MeOH-AcOEt	$C_{14}H_{17}N_3SCl_2 \cdot \frac{1}{6}CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}OC_2H_5$	52.57 52.47	2.39 2.54	12.77 12.88	9.74 9.68	Cl 21.55 Cl 21.55
C_{11}	8-Cl	H		316-318	color-less	EtOH-AcOEt	$C_{15}H_{10}N_3ClF$	64.55 64.54	3.05 3.20	14.11 14.10		Cl 11.91. F 6.38 Cl 11.83. F 6.27
C_{11}	H	H		290-291(d)	color-less	MeOH-AcOEt	$C_{15}H_{11}N_3O$	71.48 71.47	3.86 4.01	17.86 17.80		
C_{11}	H	H		325-326	color-less	EtOH	$C_{15}H_{11}N_3S$	70.08 70.16	4.50 4.65	14.42 14.36	11.00 10.87	
C_{11}	H	H		>340	color-less	EtOH	$C_{15}H_{11}N_3O \cdot \frac{1}{2}H_2O$	69.44 69.47	4.86 4.93	18.00 17.86		
C_{11}	H	H		291-293	color-less	MeOH-AcOEt	$C_{15}H_{10}N_3F$	72.99 72.62	3.83 3.88	15.96 15.83		F 7.22 F 7.28
C_{11}	H	H		259-260	color-less	MeOH-AcOEt	$C_{15}H_{10}N_3F$	72.99 72.94	3.83 4.16	15.96 15.69		F 7.22 F 7.51
C_{11}	H	H		199-201	color-less	AcOEt	$C_{15}H_{10}N_3Cl$	68.70 68.57	3.60 3.65	15.02 15.04		Cl 12.67 Cl 12.82
C_{11}	H	H		305-306	light yellow	EtOH-AcOEt	$C_{14}H_9N_3SCl$	58.85 58.58	2.82 3.16	14.71 14.43	11.22 10.95	Cl 12.41 Cl 12.52
C_{11}	H	H		233-235	color-less	AcOEt	$C_{17}H_{13}N_3O$	74.17 74.02	4.76 4.78	15.26 14.97		

Table 3 (3)

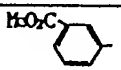
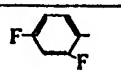
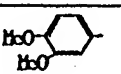
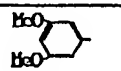
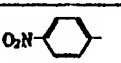
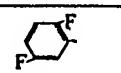
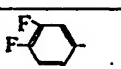
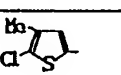
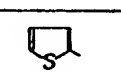
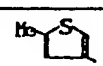
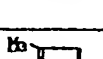
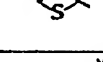
C$_{25}$	H	H		283-285	color-less	EtOH	$C_{15}H_{11}N_3S$	67.90 67.77	4.18 4.29	15.84 15.59	12.08 11.81	
C$_{26}$	H	H		251-253	color-less	AcOEt	$C_{18}H_{13}N_3O_2 \cdot \frac{1}{4}C_6H_5-\overset{O}{\overset{\|}{C}}-OC_2H_5$	70.36 70.29	4.58 4.61	13.09 13.07		
C$_{27}$	H	H		194-195	color-less	EtOH	$C_{15}H_9N_3F_2$	68.33 68.40	3.23 3.26	14.94 15.04		F 13.51 F 13.46
C$_{28}$	H	H		265-267	color-less	EtOH	$C_{19}H_{19}N_3O_2 \cdot {}^1/_6H_2O$	70.29 70.26	5.00 5.07	13.66 13.66		
C$_{29}$	H	H		291-292	color-less	EtOH	$C_{19}H_{19}N_3O_2$	70.81 71.17	4.95 4.94	13.76 13.80		
C$_{30}$	H	H		>340	Yellow	DMF	$C_{15}H_{10}N_4O_2 \cdot \frac{1}{4}H_2O$	65.19 65.48	3.59 3.74	19.01 18.91		
C$_{31}$	H	H		248-250	color-less	EtOH	$C_{15}H_9N_3F_2$	68.33 68.15	3.23 3.34	14.94 14.95		F 13.51 F 13.62
C$_{32}$	H	H		224-226	color-less	EtOH-AcOEt	$C_{15}H_9N_3F_2$	68.33 68.63	3.23 3.47	14.94 14.99		F 13.51 F 13.72
C$_{33}$	H	H		310-311	color-less	EtOH-AcOEt	$C_{15}H_9N_3F_2$	68.33 68.33	3.23 3.49	14.94 14.88		F 13.51 F 13.58
C$_{34}$	H	H		326(d)	color-less	EtOH	$C_{15}H_{10}N_3SCl$	60.10 59.74	3.36 3.63	14.02 13.71	10.69 10.61	
C$_{35}$	7-Cl	H		>310	color-less	EtOH	$C_{15}H_8N_3SCl$	58.85 58.61	2.82 3.11	14.71 14.40	11.22 11.11	

Table 3 (4)

C..	7-Cl	H		>315	color-less	CHCl₃-MeOH	C₁₈H₁₃N₃ClF	64.55 64.67	3.05 3.32	14.11 14.11		Cl 11.91 Cl 12.07
C..	H	H		295-296	color-less	EtOH-AcOEt	C₁₈H₁₅N₃S	67.90 67.84	4.18 4.35	15.84 15.64	12.08 11.87	
C..	7-Cl	H		287-289	color-less	EtOH	C₁₈H₁₄N₃SCl	60.10 60.00	3.36 3.50	14.20 13.96	10.69 10.60	
C..	7-Cl	H		307-308	color-less	EtOH	C₁₈H₁₄N₃SCl·¹/₂H₂O	59.65 59.78	3.42 3.59	13.91 14.03	10.62 10.20	
C..	8-F	H		>310	color-less	EtOH-AcOEt	C₁₈H₁₃N₃F₂	68.33 68.20	3.23 3.48	14.94 14.92		F 13.51 F 13.60
C..	8-F	H		272-274	color-less	EtOH-AcOEt	C₁₈H₁₄N₃SF	63.59 63.52	3.56 3.77	14.83 14.71	11.32 11.02	
C..	7-Me	H		323-326	color-less	EtOH-AcOEt	C₁₉H₁₇N₃S·¹/₂H₂O	67.33 67.18	4.24 4.51	15.66 15.64		
C..	7-Me	H		>315	color-less	EtOH-AcOEt	C₁₉H₁₇N₃S	68.79 68.52	4.69 4.91	15.04 14.85		
C..	7-Cl	8-Cl		>300	color-less	EtOH-AcOEt	C₁₈H₁₇N₃SCl₂	52.51 52.25	2.20 2.55	13.13 13.00	10.01 9.84	
C..	H	H		303-304.5	color-less	EtOH-AcOEt	C₁₉H₁₈N₄O	67.19 67.25	4.02 4.22	22.38 22.20		
C..	H	H		254-256	color-less	AcOEt-MeOH	C₁₉H₁₈N₄O·¹/₂H₂O	67.59 67.76	4.63 4.68	21.02 20.74		

5 10 15 20 25 30 35 40 45 50 55

Table 3 (5)

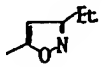
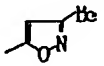
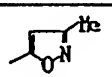
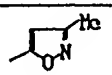
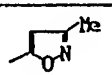
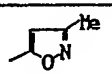
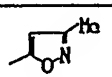
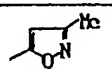
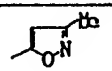
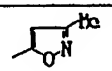
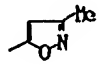
C 17	7-F	H		309-311 (d)	color-less	AcOEt-MeOH	$C_{18}H_{13}N_4OF$	63.82 63.58	3.92 4.06	19.84 19.74	
C 18	7-F	H		308-310 (d)	color-less	AcOEt-MeOH	$C_{14}H_9N_4OF$	62.68 62.46	3.38 3.50	20.88 20.67	
C 19	8-F	H		293-295	color-less	AcOEt	$C_{14}H_9N_4OF$ $\cdot {}^1/_4H_2O$	61.87 61.65	3.70 3.51	20.28 20.54	
C 20	7-MeO	H		280-282 (d)	color-less	AcOEt-MeOH	$C_{15}H_{12}N_4O_2$ $\cdot {}^1/_4AcOEt$	63.91 63.69	4.49 4.44	19.23 19.25	
C 21	7-MeO	H		303-305 (d)	color-less	AcOEt-MeOH	$C_{15}H_{12}N_4O$ $\cdot {}^1/_4H_2O$	67.40 67.36	4.65 4.67	20.96 21.02	
C 22	8-Cl	H		310-311 (d)	light yellow	AcOEt-MeOH	$C_{14}H_9N_4OCl$ $\cdot {}^5/_4H_2O$	55.96 56.08	3.58 3.72	18.64 18.57	
C 23	7-Cl	8-F		322-325 (d)	color-less	AcOEt-MeOH	$C_{14}H_8N_4OClF$ $\cdot {}^1/_2H_2O$	53.43 53.40	2.99 3.26	17.80 17.68	
C 24	7-Cl	H		319-321 (d)	color-less	AcOEt-MeOH	$C_{14}H_9N_4OCl$ $\cdot CH_3OH$	56.87 56.62	4.13 4.29	17.68 17.54	Cl:11.19 Cl:11.07
C 25	7-CF_3	H		295-297 (d)	color-less	AcOEt	$C_{15}H_9N_4OF_3$	56.60 56.58	2.85 3.05	17.60 17.61	
C 26	7-Cl	9-Cl		256-258	color-less	EtOH	$C_{14}H_8N_4OCl_2$	52.68 52.40	2.53 2.62	17.56 17.41	Cl:22.22 Cl:22.42
C 27	6-F	H		275-277 (d)	color-less	AcOEt-EtOH	$C_{14}H_9N_4OF$	62.68 62.49	3.38 3.63	20.88 20.82	

Table 3 (6)

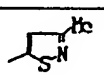
C..	H	H		271-274 (d)	color-less	AcOEt	$C_{13}H_8N_4O \cdot {}^1/_4H_2O$	65.47 65.41	3.49 3.74	23.49 23.28	
C..	7-Cl	H		302-306 (d)	color-less	MeOH-CHCl$_3$	$C_{13}H_7N_4OCl \cdot {}^1/_4H_2O$	57.21 57.20	2.68 2.94	20.53 20.36	
C..	7-F	H		297-299	color-less	AcOEt-MeOH	$C_{13}H_7N_4OF \cdot {}^1/_4H_2O$	60.70 60.96	2.87 3.17	21.78 21.73	
C..	H	H		273-274	color-less	AcOEt	$C_{14}H_{10}N_4O$	67.19 67.23	4.02 4.22	22.38 22.20	
C..	7-F	H		328-330 (d)	color-less	AcOEt-EtOH	$C_{14}H_9N_4OF$	62.68 62.61	3.38 3.58	20.88 20.68	
C..	H	H		268-269	color-less	AcOEt	$C_{15}H_{12}N_4O$	68.17 68.16	4.57 4.74	21.19 21.01	
C..	7-F	H		307-310 (d)	color-less	AcOEt-EtOH	$C_{15}H_{11}N_4OF$	63.82 63.74	3.92 4.08	19.84 19.68	
C..	8-F	H		312-315 (d)	color-less	AcOEt-MeOH	$C_{14}H_9N_4OF$	62.68 62.56	3.38 3.56	20.88 20.66	
C..	7-Cl	H		344-347 (d)	color-less	MeOH	$C_{14}H_9N_4OCl$	59.06 58.78	3.18 3.22	19.67 19.44	
C..	H	H		274-275	color-less	AcOEt-EtOH	$C_{14}H_{10}N_4S \cdot {}^1/_4H_2O$	62.30 62.56	3.88 4.12	20.76 20.62	
C..	H	H		309-310 (d)	color-less	AcOEt-EtOH	$C_{14}H_{10}N_4S \cdot {}^1/_4H_2O$	62.43 62.68	3.87 4.15	20.80 20.89	

Table 3 (7)

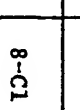
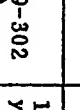
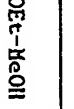
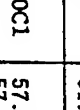
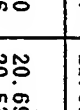
C ₂₂	H	H		296-298	color-less	MeOH	$C_{13}H_9N_3O$	57.98 58.18	4.12 3.98	26.01 25.90	
C ₂₃	H	H		290-293 (d)	color-less	MeOH	$C_{14}H_{11}N_3S \cdot H_2O$	53.13 53.30	3.34 3.39	25.81 25.54	S:11.81 S:11.69
C ₂₁	H	H		303-305 (d)	color-less	MeOH-AcOEt	$C_{14}H_{11}N_3S$	63.13 63.29	3.78 3.80	21.03 20.83	
C ₂₂	H	H		245-246 (d)	color-less	AcOEt-hexane	$C_{14}H_{11}N_3S \cdot 1/_8H_2O$	62.61 62.89	3.85 4.00	20.86 20.57	
C ₂₂	H	H		292-294 (d)	color-less	AcOEt-MeOH	$C_{13}H_9N_3S$	61.88 61.94	3.19 3.30	22.20 21.97	
C ₂₂	H	H		242-244	color-less	AcOEt	$C_{13}H_9N_3S \cdot 1/_8H_2O$	61.02 61.27	3.31 3.57	21.89 21.81	
C ₂₂	H	H		276-278	color-less	EtOH-AcOEt	$C_{14}H_{11}N_5 \cdot 1/_8H_2O$	66.50 66.65	4.54 4.73	27.69 27.47	
C ₂₂	H	H		263-265	color-less	EtOH-AcOEt	$C_{14}H_{11}N_5$	67.46 67.56	4.45 4.74	28.09 27.85	
C ₂₂	H	H		251-253	color-less	EtOH-AcOEt	$C_{14}H_{11}N_3O$	67.19 67.29	4.03 4.09	22.39 22.13	
C ₂₂	H	H		242-243	color-less	AcOEt	$C_{13}H_9N_3S \cdot 1/_8H_2O$	61.02 61.27	3.31 3.57	21.89 21.81	
C ₂₂	8-Cl	H		299-302 (d)	light yellow	AcOEt-MeOH	$C_{13}H_7N_3OCl$	57.68 57.69	2.60 2.76	20.69 20.53	

Table 3 (8)

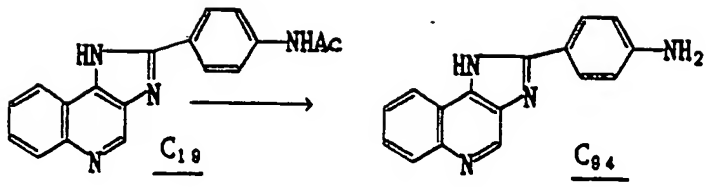
C..	8-F	H		308-310 (d)	color-less	MeOH-AcOEt	$C_{..}H_{..}N_{..}OF$	61.41 61.71	2.77 3.03	22.03 21.91	
C..	8-F	H		308-310.5 (d)	color-less	MeOH-AcOEt	$C_{..}H_{..}N_{..}FO$	61.41 61.63	2.77 3.03	22.03 21.86	
C..	8-OMe	H		279-281 (d)	color-less	MeOH-AcOEt	$C_{..}H_{..}N_{..}O_{..}$ $\cdot {}^{1}/_{..}H_{..}O$	62.10 62.19	3.93 3.92	20.69 20.69	
C..	7-F	H		316-319 (d)	color-less	MeOH-AcOEt	$C_{..}H_{..}N_{..}FO$ $\cdot {}^{1}/_{..}H_{..}O$	60.88 61.02	2.85 3.13	21.85 21.77	
C..	6-F	H		329-332 (d)	color-less	MeOH-$CH_{..}Cl_{..}$	$C_{..}H_{..}N_{..}FO$	61.41 61.59	2.77 3.02	22.03 21.99	
C..	7-Me	H		294-297.5 (d)	color-less	AcOEt	$C_{..}H_{..}N_{..}O$	67.19 67.27	4.02 4.03	22.38 22.41	
C..	7-$CF_{..}$	H		324-328 (d)	color-less	MeOH-AcOEt	$C_{..}H_{..}N_{..}F_{..}O$	55.27 55.43	2.31 2.56	18.41 18.40	
C..	9-F	H		277-279	color-less	MeOH-AcOEt	$C_{..}H_{..}N_{..}OF$	61.41 61.51	2.77 3.02	22.03 21.90	
C..	9-F	H		282-284.5 (d)	color-less	MeOH-AcOEt	$C_{..}H_{..}N_{..}FS$	62.44 62.66	2.99 3.26	15.60 15.69	
C..	6-F	H		320-322	color-less	EtOH	$C_{..}H_{..}N_{..}SF$	62.44 62.25	2.99 3.22	15.60 15.36	
C..	9-Cl	H		210-212	color-less	MeOH	$C_{..}H_{..}N_{..}OCl$ $\cdot {}^{1}/_{..}CH_{..}OH$	56.55 56.69	3.16 2.97	19.55 20.03	Cl: 12.37 12.51

Table 3 (9)

C_{11}	9-Cl	H		243-245	color-less	MeOH	$C_{17}H_{11}N_3SCl$	58.84 58.79	2.82 3.02	14.71 14.86	Cl:12.41, S:11.22 Cl:12.30, S:10.96
C_{11}	9-Cl	H		202-203	color-less	MeOH	$C_{17}H_{11}N_3SCl$	60.09 59.88	3.36 3.50	14.02 14.00	Cl:11.83, S:10.70 Cl:11.86 S:10.64
C_{11}	9-F	H		292-294	color-less	AcOEt-MeOH	$C_{17}H_{11}N_3OF$	62.68 62.83	3.38 3.52	20.88 20.84	

Example 94

2-(4-Aminophenyl)-1H-imidazo[4,5-c]quinoline C_{16}



A suspension of 320 mg of 2-(4-acetylaminophenyl)-1H-imidazo[4,5-c]quinoline C19 in 10 mlof 1N sodium hydroxide is refluxed for 1.5 hours. After the mixture is cooled and neutralized with acetic acid, the resulting white crystals are filtered, washed successively with water and ethanol, and dried to give 195 mg - (71%) of C84.
m.p. ca. 340°C (from ethanol)
Anal. Calcd.(%) (for $C_{16}H_{12}N_4 \cdot 1/8C_2H_5OH$)
: C, 73.36; H, 4.83; N, 21.06.
Found (%) : C, 73.44; H, 4.93; N, 20.95.

Example 95

2-(4-methylphenyl)-1H-imidazo[4,5-c]quinoline C95

A suspension of 326 mg of 4-methylbenzoic acid and 318 mg of 3,4-diaminoquinoline A1 in 10 g of polyphosphoric acid is heated with stirring at 180°C for 4 hours. The cooled mixture is poured into ice-water and neutralized with aqueous sodium hydroxide. The resulting solid is chromatographed on silica gel with chloroform -methanol (25:1 v/v) as eluent to give 430 mg (83%) of C95 as white crystals.
m.p.: 326 -329°C (dec.) (from ethanol)
Anal. Calcd. (%) (for $C_{17}H_{13}N_3 \cdot 1/3H_2O$)
: C, 76.96; H, 5.19; N, 15.84.
Found (%) : c, 76.86; H, 4.84; N, 15.52.

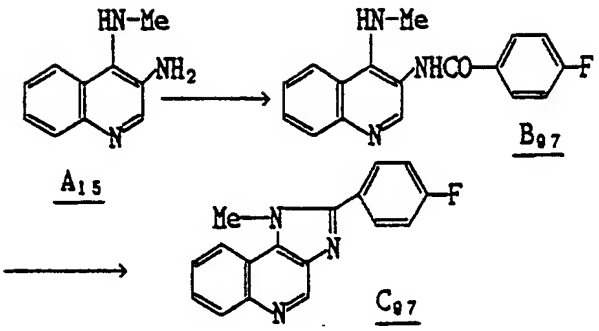
Example 96

2-(4-Chlorophenyl)-1H-imidazo[4,5-c]quinoline C96

A suspension of 239 mg of 4-chlorobenzoic acid and 470 mg of 3,4-diaminoquinoline A1 in 9 g of polyphosphoric acid is heated at 185°C for 4 hours with stirring under nitrogen. The same work-up as described in Example 95 gives 248 g (59%) of C96 as white crystals.
m.p. 335 -337°C(dec.)(from ethanol)
Anal.Calcd. (%) (for $C_{16}H_{10}N_3Cl$)
: C, 68.70; H, 3.60; N, 15.02; Cl, 12.68.
Found (%) : C, 68.42; H, 3.71; N, 14.83; Cl, 12.76.

Example 97

2-(4-Fluorophenyl)-1-methyl-1H-imidazo[4,5-c]quinoline C97



To a solution of 390 mg of 4-fluorobenzoic acid in 6 ml of anhydrous hexamethylphosphoramide and 0.6 ml of anhydrous acetonitrile is added dropwise 320 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at the same temperature for 30 minutes, a solution of 440 mg of 3-amino-4-methylaminoquinoline A_{15} in 4 ml of anhydrous hexamethylphosphoramide is added and stirred at 0°C for 2.5 hours. The same work-up as described in Example 1 gives 750 kg of B_{97} as a white solid. It is dissolved in 10 ml of acetic acid and refluxed for 1 hour. The mixture is concentrated under reduced pressure and the residue is shaken with ethyl acetate -saturated aqueous sodium bicarbonate. The organic layer is separated, washed successively with water and aqueous sodium chloride, and dried. The solvent is evaporated and the residue is crystallized from n-hexane to give 610 mg (87%) of C_{97} as white crystals.

m.p. : 185 -187°C (from ethyl acetate)

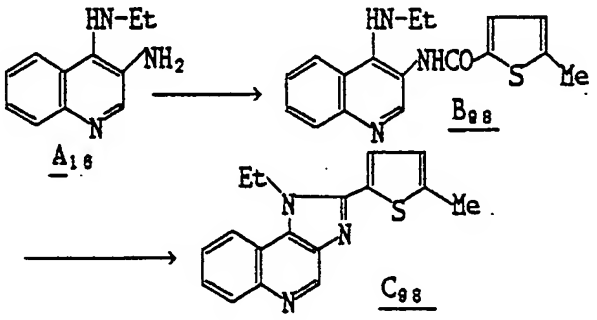
Anal. Calcd. (%) (for $C_{17}H_{12}N_3F$)

: C, 73.63; H, 4.36; N, 15.15; F, 6.85.

Found (%) : C, 73.73; H, 4.36; N, 15.15; F, 6.77.

Example 98

1-Ethyl-2-(5-methylthien-2-yl)-1H-imidazo[4,5-c]quinoline C_{98}



To a solution of 270 mg of 5-methylthiophene-2-carboxylic acid in 5 ml of anhydrous hexamethylphosphoramide and 0.5 ml of anhydrous acetonitrile is added dropwise 215 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at the same temperature for 30 minutes, a solution of 320 mg of 3-amino-4-ethylaminoquinoline A_{16} in 0.5 ml of anhydrous hexamethylphosphoramide is added and stirred at 0 -5°C for 3 hours. The same work-up as described in Example 1 gives 510 mg of B_{98} as a white solid. It is suspended in 10 ml of acetic acid and refluxed for 1 hour. The mixture is concentrated and the residue is shaken with ethyl acetate-saturated aqueous sodium bicarbonate. The organic layer is separated, washed successively with water and saturated aqueous sodium chloride, and dried. The solvent is evaporated and the residue is chromatographed on silica gel with chloroform -methanol (20:1 v/v) as eluent to give 380 mg -(76%) of C98 as colorless crystals.

m.p.: 205 -206°C(dec.) (from ethyl acetate)

Anal. Calcd. (%) for $C_{17}H_{15}N_3S$)
: C, 69.60; H, 5.15; N, 14.32; S, 10.93.
Found (%) : C, 69.66; H, 4.96; N, 14.30; S, 10.88.

Example 99

2-(4-Methyloxazol-5-yl)-1H-imidazo[4,5-c]quinoline C$_{99}$

To a solution of 300 mg of 4-methyloxazole-5-carboxylic acid in 4 ml of hexamethylphosphoramide and 0.4 ml of acetonitrile is added 268 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at the same temperature for 30 minutes, 340 mg of 3,4-diaminoquinoline A$_1$is added and stirred at 0 -5°C for 3 hours. The mixture is diluted with ice-water and neutralized with saturated aqueous sodium bicarbonate. The resulting solid is filtered and washed with water to give 425 mg of 4-amino-3-(4-methylisoxazole-5-ylcarbonylamino)quinoline as crude crystals. It is suspended in 12 ml of Dowtherm A (Dow Chemical Co.) and refluxed for 2.5 hours. The cooled mixture is diluted with 50 ml of n-hexane and the resulting solid is collected by filtration. It is chromatographed on silica gel with dichloromethane -methanol (20:1 v/v) as eluent to yield a crude solid which is recrystallized from ethyl acetate -methanol, giving 297 mg of C$_{99}$ as pale yellow crystals.
m.p. 289 -292°C (dec.)
Anal. Calcd. (%) (for $C_{14}H_{10}N_4O \cdot 1/8H_2O$)
: C, 66.59; H, 4.09; N, 22.19.
Found (%) : C, 66.86; H, 4.18; N, 21.98.

Example 100

2-(3-Methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline hydrochloride C$_{100}$

To an ethanolic solution of 300 mg of 2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline C$_{99}$ is added ethanolic hydrogen chloride at room temperature. The mixture is evaporated and the residue is washed with acetone to give C$_{100}$ as crystals melting at 248.5 -252°C (dec.).
Anal. Calcd. (%) (for $C_{14}H_{11}N_4OCl \cdot 1/3H_2O$)
: C, 57.45; H, 4.02; N, 19.14; Cl, 12.11
Found (%) : C, 57.64; H, 4.27; N, 18.90; Cl, 12.23

Example 101

3-Methanesulfonyl-2-(3-methylisoxazol-5-yl)-3H-imidazo[4,5-c]quinoline C$_{101}$

To a solution of 300 mg of 2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline C$_{99}$ in 20 ml of tetrahydrofuran is added 50 mg of 60% sodium hydride in mineral oil and stirred at 75°C for 2 hours under nitrogen. To the cooled mixture is added dropwise 180 mg of methanesulfonyl chloride and stirred at 0 -5°C for 2 hours. The mixture is concentrated under reduced pressure and the residue is poured into ice-water. The resulting solid is collected by filtration and chromatographed on silica gel with dichloromethane - methanol (50:1 v/v) as eluent, yielding 159 mg (40%) of C$_{101}$ as white crystals.
m.p. 167.5 -169°C (dec.) (from ethyl acetate)
Anal. Calcd. (%) (for $C_{15}H_{12}N_4O_3S$)
: C, 54.86; N, 3.68; N, 17.06
Found (%) : C, 54.95; H, 3.97; N, 16.79

Example 102

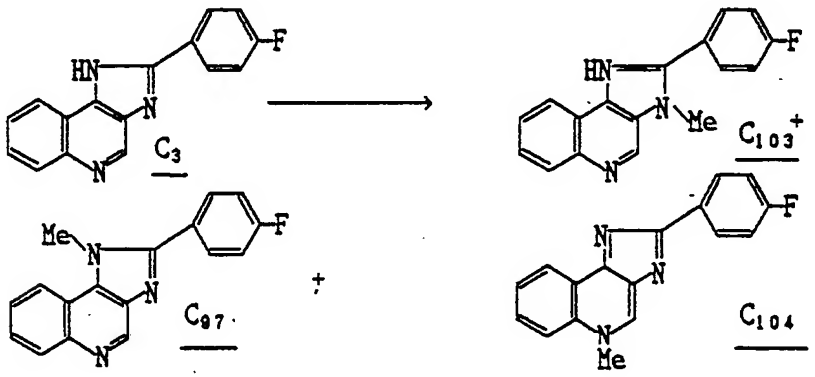
1-Methyl-2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline C_{102}

To a solution of 245 mg of 3-methylisoxazole-5-carboxylic acid in 20 ml of hexamethylphosphoramide and 0.4 ml of acetonitrile is added 226 mg of thionyl chloride at -5 -0°C. After stirring at the same temperature for 30 minutes, 330 mg of 3-amino-4-methylaminoquinoline A_{15} is added and stirred at 0 - 5°C for 5 hours. The mixture is diluted with 50 ml of ice-water and neutralized with saturated aqueous sodium bicarbonate. The resulting solid is filtered and washed with water to give 361 mg (67%) of 4-methylamino-3-[(3-methylisoxazole-5-ylcarbonyl)amino]quinoline. It is suspended in 4 ml of hexamethylphosphoramide and 1 ml of acetic acid and stirred at 180°C (bath temperature) for 40 minutes. The cooled mixture is poured into ice-water and neutralized with aqueous sodium bicarbonate. The resulting solid is filtered, washed with water and chromatographed on silica gel with dichloromethane -methanol (25:1 v/v) as eluent. The product obtained is recrystallized from dichloromethane -methanol to give 294 mg of C_{102} as white crystals melting at 281 -284°C (dec).

Anal. Calcd. (%) (for $C_{15}H_{12}N_4O$)
: C, 68.17; H, 4.57; N, 21.19.
Found (%) : C, 68.29; N, 4.57; N, 21.21.
NMR ($CDCl_3$-CD_3OD):δ2.46(s,3H), 4.57(s,3H), 6.99(s,1H), 7.6-8.7(m,4H), 9.23(s,1H).

Example 103

2-(4-Fluorophenyl)-3-methyl-3H-imidazo[4,5-c]quinoline C_{103} 2-(4-Fluorophenyl)-1-methyl-1H-imidazo[4,5-c]-quinoline C_{97} and 2-(4-Fluorophenyl)-5-methyl-5H-imidazo[4,5-c]quinoline C_{104}



To a solution of sodium ethoxide (prepared from 70 mg of metallic sodium and 10 ml of anhydrous ethanol) is added 520 mg of 2-(4-fluorophenyl)-1H-imidazo[4,5-c]quinoline C_3 at room temperature under nitrogen and stirred for 5 minutes. To the mixture is added 0.5 ml of methyl iodide and stirred at 50°C for 1 hour. The mixture is poured into ice-water and extracted with ethyl acetate. The extract is washed with water and dried. Evaporation of the solvent gives a residue which is chromatographed on silica gel with chloroform -methanol (30:1 v/v) as eluent. The fractions containing the compound with an Rf = 0.35 are combined and evaporated to give 90 mg (16%) of 3-methyl derivative C_{103} as colorless crystals.

m.p 168 -170°C (ethyl acetate -n-hexane)
Anal. Calcd. (%) (for $C_{17}H_{12}N_3F$)
: C, 73.63; H, 4.36; N, 15.15; F, 6.85.
Found (%) : C, 73.86; H, 4.56; N, 15.13; F, 6.86.
NMR ($CDCl_3$) : δ4.02(s,2H), 7.17-8.77(m,8H), 9.10(s,1H)

Then evaporation of the combined fractions containing the product with an Rf = 0.27 yields 60 mg - (11%) of 1-methyl derivative C_{97} which is identical with the compound obtained in Example 97.

Lastly the combined fractions containing the compound with an Rf = 0.12 is evaporated to give 340 mg - (62%) of 5-methyl derivative C_{104} as colorless crystals.
m.p. 277 -278°C(from ethyl acetate -methanol)
Anal. Calcd. (%) (for $C_{17}H_{12}N_3F$)
: C, 73.63; N, 4.36; N, 15.15; F, 6.85.
Found (%) : C, 73.64; H, 4.36; N, 15.05; F, 6.76.
NMR ($CDCl_3$):δ4.23(s,3H), 7.03-8.93(m,8H), 8.56(s,1H).

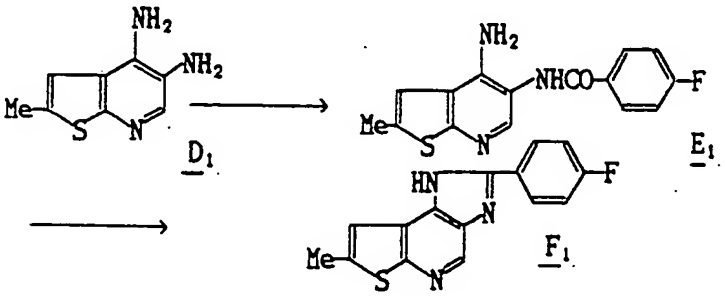
Example 104

3-Methyl-2-(3-methylisoxazol-5-yl)-3H-imidazo[4,5-c]quinoline C_{105},1-Methyl-2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline C_{107} and 5-Methyl-2-(3-methylisoxazol-5-yl)-5H-imidazo[4,5-c]quiniline C_{106}

To a solution of 450 mg of 2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline C_{65} in 39 ml of tetrahydrofuran is added 80 mg of 60% sodium hydride in mineral oil and stirred at 60°C for 1.5 hours under nitrogen. To the cooled mixture is added dropwise 385 mg of methyl iodide in 2 ml of tetrahydrofuran at 0 -5°C. After stirring at 0 -5°C for 30 minutes and then at 40°C for 4 hours, the mixture is evaporated and the residue is chromatographed on silica gel with dichloromethane -methanol (50:1 v/v) as eluent, to give 58 mg (12%) of 3-methyl derivative C_{105} as white crystals.
m.p. 179.5 - 182°C (from ethyl acetate)
Anal. Calcd. (%) (for $C_{15}H_{12}N_4 \cdot 1/4H_2O$)
: C, 67.03; H, 4.69; N, 20.84.
Found (%) : C, 67.16; N, 4.98; N, 20.62.
NMR ($CDCl_3$-CD_3OD):δ2.46(s,3H), 4.35(s,3H), 7,13(s,1H), 7.6 -8.7 (m,4H), 9.13 (s,1H).
The further elution with the same solvent yields 42 mg (9%) of 1-metyl derivative C_{107} which is identical with the compound described in Example 102.
Then the eluate with dichloromethane -methanol (25:1 v/v) affords 322 mg (68%) of 5-methyl derivative C_{106} as white crystals.
m.p.: 308 -309°C (dec.) (from ethyl acetate -methanol)
Anal.Calcd. (%) (for $C_{15}H_{12}N_4O$)
: C, 68.17; H, 4.57; N, 21.19.
Found (%) : C, 68.14; H. 4.76; N, 21.12.
NMR ($CDCl_3$-CD_3OD):δ2.42(s,3H), 4.40(s,3H), 6.99(s,1H), 7.6-8.9 (m,4H), 9.07(s,1H).

Example 105

2-(4-Fluorophenyl)-7-methyl-1H-imidazo[4,5-c]thieno[2,3-b]pyridine F,

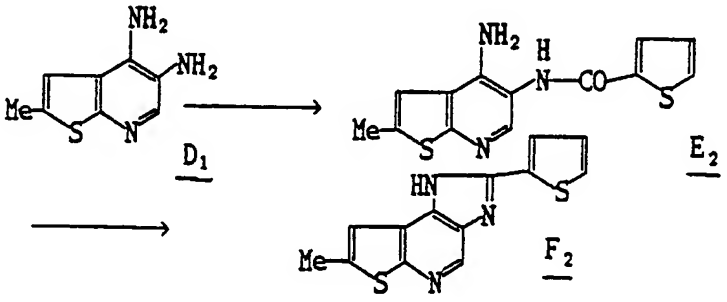


To a solution of 308 mg of 4-fluorobenzoic acid in 5 ml of anhydrous hexamethylphosphoramide and 0.5 ml of anhydrous acetonitrile is added dropwise 250 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at the same temperature for 30 minutes, 358 mg of diaminothienopyridine D_1 is added and stirred at 0 -5°C for 3 hours. The mixture is diluted with ice-water and neutralized with saturated aqueous

sodium bicarbonate. The resulting crystals are filtered, washed with water and dried to yield 630mg of 4-amino-2-methyl-5-(4-fluorobenzoylamino)thieno[2,3-b]pyridine E_1. It is suspended in 15 ml of polyphosphoric acid and heated at 140°C with stirring under nitrogen. The cooled mixture is poured into ice-water and neutralized with aqueous sodium hydroxide. The product is extracted with ethyl acetate and the extract is washed with water, dried and evaporated. The residue is chromatographed on silica gel with chloroform-methanol (25:1 v/v) as eluent to afford 457 mg (81%) of F_1 as colorless crystals.
m.p.: 313 -316°C (from ethanol)
Anal.Calcd. (%) (for $C_{15}H_{10}N_3SF$)
: C, 63.58; H, 3.55; N, 14.83; S, 11.31.
Found (%) : C, 63.32; H, 3.79; N, 14.61; S, 11.09.

Example 106

2-(Thien-2-yl)-7-methyl-1H-imidazo[4,5-d]thieno[2,3-b]pyridine F_2

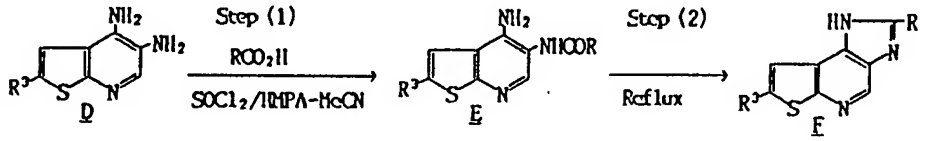


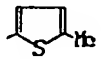
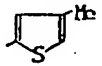
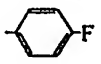
To a solution of 212 mg of thiophene-2-carboxylic acid in 4 ml hexamethylphosphoramide and 0.4 ml of acetonitrile is added dropwise 188 mg of thionyl chloride at -5 -0°C under nitrogen. After stirring at 0 -5°C for 30 minutes, 269 mg of diaminothienopyridine D_1 is added and stirred at 0 -5 °C for 3 hours. The same work-up as described in Example 105 gives 403 mg of E_2 as crude crystals. It is suspended in 20 ml of Dowtherm A (Dow Chemical Co.) and refluxed for 3 hours under nitrogen. The cooled mixture is diluted with n-hexane and the resulting crystals are filtered. It is chromatographed on silica gel with chloroform - methanol (25:1 v/v) as eluent to give 286 mg (70%) of F_2 as colorless crystals.
m.p. : 284 -287°C (from methanol -ethyl acetate)
Anal. Calcd. (%) (for $C_{13}H_9N_3S_2$)
: C, 57.54; H, 3.34; N, 15.48; S, 23.68.
Found (%) : C, 57.46; H, 3.60; N, 15.39; S, 23.67.

Example 107-114

According to the method illustrated by Example 106, Compounds F_3-F_{10} are obtained under the conditions shown in Table 4. Table 5 shows the physical properties of these componds.

Table 4

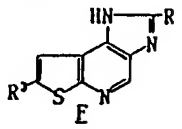


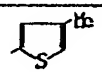
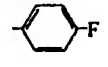
Ex. No.	R^3	R	Step (1)					Compound E	Step (2)			Compound F	
			RCO2H (mg)	SOCl2 (mg)	HMPA–MeCN (ml) (ml)	Yield of D (mg)	Reaction time (brs.)		Yield of E (mg)	Dowtherm A (ml)	Reaction time (brs.)	Yields (mg)	Compd. No.
107	Me		213	190	4 - 0.4	270	4	390	370	7.4	2	310	F,
108	Me		199	160	4 - 0.4	230	4	375	350	7	3	310	F,
109	Me		199	160	4 - 0.4	230	4	372	350	7	3.5	305	F,
110	Me		199	160	4 - 0.4	230	4	355	330	6.6	16	250	F,
111	H		214	191	4 - 0.4	250	3.5	387	370	7.4	2	315	F,
112	H		214	191	4 - 0.4	250	3.5	378	350	7	2	300	F,
113	H		215	174	4 - 0.4	230	3.5	300	280	5.6	2	240	F,
114	Me		229	230	4 - 0.4	330	5	514	510	10	1	362	F,,

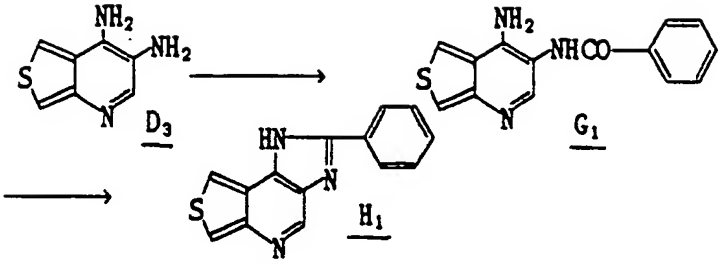
Example 115

2-Phenyl-1H-imidazo[4,5-d]thieno[3,4-b]pyridine H,

Table 5



Compd. No.	R³	R	m.p. (°C)	Appearance	Solvent for crystalln.	Molecular Formula	Elementary Analysis (%) Up (Calcd.). Down (Found)		
							C	H	N
F₃	Me		295-296	colorless	MeOH-AcOEt	$C_{13}H_9N_3S_2$	57.54 57.44	3.34 3.61	15.48 15.46
F₄	Me		277-278	colorless	EtOH-Et₂O	$C_{14}H_{11}N_3S_2 \cdot \frac{1}{5}H_2O$	58.46 58.49	3.94 4.12	14.61 14.56
F₅	Me		268-270	colorless	EtOH-Et₂O	$C_{14}H_{11}N_3S_2$	58.92 58.82	3.88 3.99	14.72 14.66
F₆	Me		263-266	colorless	EtOH-Et₂O	$C_{14}H_{11}N_3S_2$	58.92 58.73	3.88 4.11	14.72 14.81
F₇	H		290-293	colorless	AcOEt-n-hexane	$C_{13}H_9N_3S_2 \cdot \frac{1}{4}AcOEt \cdot \frac{1}{5}H_2O$	54.72 54.83	3.41 3.61	14.73 14.59
F₈	H		277-279	colorless	AcOEt-n-hexane	$C_{13}H_9N_3S_2 \cdot \frac{1}{4}AcOEt$	55.94 55.60	3.00 3.23	15.65 15.59
F₉	H		307-310	colorless	AcOEt	$C_{14}H_9N_3SF \cdot \frac{1}{5}AcOEt$	62.13 62.32	3.23 3.35	14.99 15.25
F₁₀	Me		297-299	colorless	AcOEt-MeOH	$C_{14}H_9N_4OS$	56.23 55.99	3.14 3.35	21.86 21.70



To a solution of 189 mg of benzoic acid in 5 ml of anhydrous hexamethylphosphoramide and 0.5 ml of anhydrous acetonitrile is added dropwise 174 mg of thionyl chloride at 0°C under nitrogen. After stirring at 0°C for 30 minutes, 239 mg of diaminothienopyridine D_3 is added and stirred for 3 hours. The mixture is diluted with ice-water and neutralized with aqueous sodium bicarbonate. The resulting crystals are filtered, washed with water and dried to give 280 mg of G_1. It is suspended in 4.2 ml of hexamethylphosphoramide and 1.1 ml of acetic acid, and heated at 170°C for 30 minutes. The cooled mixture is diluted with ice-water and extracted with ethyl acetate, and the extract is washed with water and dried. After the solvent is evaporated, the residue is chromatographed on silica gel with chloroform -methanol (50:2 v/v) to give 170 mg (51%) of H_1 as colorless crystals.
m.p. 308 -312°C (dec.) (from ethyl acetate -methanol)
Anal. Calcd. (%) (for $C_{14}H_9N_3S \cdot 1/3H_2O$)
: C, 65.35; H, 3.79; N, 16.33.
Found (%) : C, 65.29; H, 3.73; N, 16.13.

Example 116

2-(4-Fluorophenyl)-1H-imidazo[4,5-d]thieno[3,4-b]pyridine H_3

According to the method illustrated by Example 115, 240 mg (50%) of H_3 is obtained from 281 mg of 4-fluorobenzoic acid and 300 mg of diaminothienopyridine D_3.
m.p. : 302 -305°C (from methanol -ethyl acetate)
Anal. Calcd. (%) (for $C_{14}H_8N_3SF$)
: C, 62.44; H, 2.99; N, 15.60.
Found (%) : C, 62.23; H, 3.26; N, 15.28.

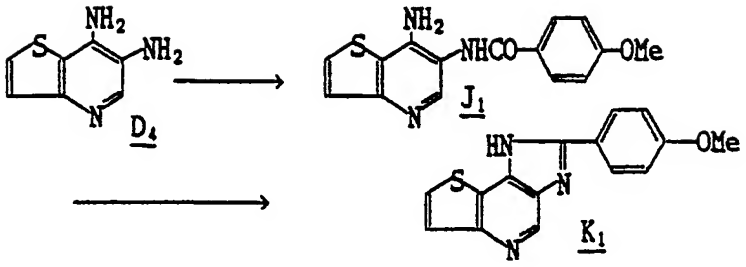
Example 117

2-(5-Chlorothien-2-yl)-1H-imidazo[4,5-d]thieno[3,4-b]pyridine H_5

According to the method illustrated by Example 115, 259 mg of H_5 is obtained from 325 mg of 5-chlorothiophene-2-carboxylic acid and 300 mg of diaminothienopyridine D_3.
m.p. : 301 -304°C (dec.)
Anal. Calcd. (%) (for $C_{12}H_6N_3ClS_2$)
: C, 49.39; H, 2.07; N, 14.40.
Found (%) : C, 49.09; H, 2.17; N, 14.16.

Example 118

2-(4-Methoxylphenyl)-1H-imidazo[4,5-d]thieno[3,2-b]pyridine K,



To a solution of 233 mg of 4-methoxybenzoic acid in 4 ml of hexamethylphosphoramide and 0.4 ml of acetonitrile is added 174 mg of thionyl chloride at 0°C under nitrogen. After stirring at 0°C for 30 minutes, 230 mg of diaminothienopyridine $\underline{D_4}$ is added and stirred at 0°C for 4 hours. The mixture is diluted with ice-water and neutralized with aqeuous sodium bicarbonate. The resulting crystals are filtered, washed with water and dried to yield 348 mg (84%) of $\underline{J_1}$. The mixture of $\underline{J_1}$ and 6.6 ml of Dowtherm A (Dow Chemical Co.) is refluxed for 2 hours. The cooled mixture is diluted with n-hexane and allowed to stand to give 300 mg (95%) of $\underline{K_1}$ as colorless crystals.

m.p. : 285 -287°C (from ethyl acetate -methanol)

Anal. Calcd. (%) (for $C_{15}H_{11}N_3OS \cdot 1/5CH_3COOC_2H_5$)

: C, 63.48; H, 4.25; N, 14.06.

Found (%) : C, 63.20; H, 4.38, N, 13.86.

Example 119 -123

According to the method illustrated by Example 118, Compounds $\underline{K_2}$-$\underline{K_5}$ are prepared under the conditions shown in Table 6. Table 7 shows the physical properties of these compounds.

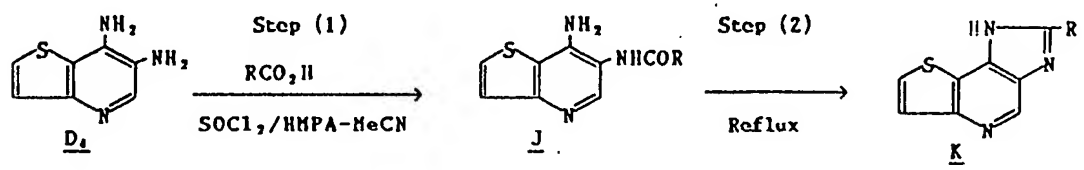


Table 6

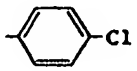
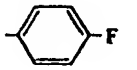
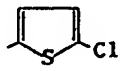
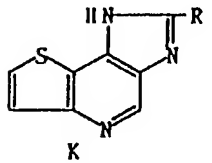
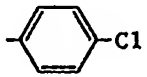
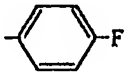
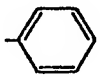
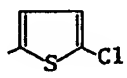
Example No.	R	Step (1)					Compound J	Step (2)			Compound K	
		RCO_2H (mg)	$SOCl_2$ (mg)	HMPA – MeCN (ml) (ml)	Yield of D_4 (mg)	Reaction time (hr.)	(mg)	Yield of J (mg)	Dowtherm A (ml)	Reaction time (hr.)	Yield (mg)	Compd. No.
119		239	174	4 - 0.4	230	4.0	365	350	7	1.5	320	K_3
120		308	250	6 - 0.6	330	3.0	475	400	8	1.5	347	K_3
121		268	250	6.6 -0.7	330	3.0	458	440	9	1.5	373	K_4
122		282	250	6 - 0.6	330	3.5	510	500	10	2	438	K_3
123		260	181	4 - 0.4	240	3.5	373	350	7	2	310	K_6

Table 7



K

Compound No.	R	m.p. (°C)	Appearance	Solvent for crystalln.	Molecular Formula	Elementary Analysis (%) Up (Calcd.), Down (Found)		
						C	H	N
K₁		334-337	colorless	MeOH-AcOEt	$C_{14}H_9N_3ClS \cdot \frac{1}{4}H_2O$	57.93 58.11	2.95 3.20	14.48 14.35
K₂		275-278	colorless	AcOEt	$C_{14}H_9N_3SF \cdot \frac{1}{4}H_2O$	61.41 61.70	3.13 3.41	15.35 14.99
K₃		288-293	colorless	MeOH-AcOEt	$C_{14}H_9N_3S$	66.91 66.66	3.60 3.86	16.72 16.59
K₄		281-285	colorless	MeOH-AcOEt	$C_{12}H_7N_3ClS_2 \cdot \frac{1}{4}H_2O$	55.36 55.51	2.84 3.03	16.14 15.86
K₅		224-228	colorless	MeOH-AcOEt	$C_{13}H_8N_3ClS_2 \cdot \frac{1}{4}CH_3OH$	49.07 49.03	2.35 2.64	14.01 14.06

3,4-Diaminoquinolines

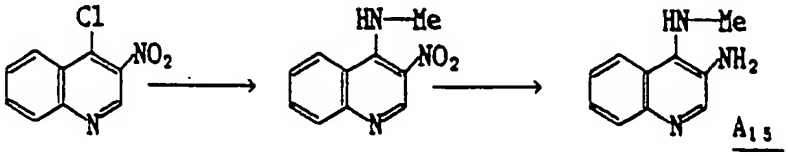
The starting 3,4-diaminoquinolines are prepared by sequential chlorination, amination and reduction of 3-nitro-4-hydroxyquinolines according to the literature [G. B. Bachman et al., J. Am. Chem. Soc., 69, 365 - (1947) and A. R. Surrey et al., J. Am. Chem. Soc., 73, 2413 (1951)].

The following table shows their melting points.

Comp.No.	R_1	R_2	mp (°C)
A_1	H	H	168 - 170 (dec.)
A_2	6-Cl	H	206 - 209 (dec.)
A_3	7-Cl	H	193 - 195 (dec.)
A_4	6-F	H	196 - 198 (dec.)
A_5	7-Me	H	155 - 158
A_6	6-Cl	7-Cl	250 - 253 (dec.)
A_7	7-F	H	185 - 188 (dec.)
A_8	7-MeO	H	136 - 139 (dec.)
A_9	7-CF_3	H	179 - 181 (dec.)
A_{10}	6-F	7-Cl	249 - 252 (dec.)
A_{11}	5-Cl	7-Cl	200 - 203 (dec.)
A_{12}	5-Cl	H	157 - 159
A_{13}	8-F	H	167 - 169 (dec.)
A_{14}	5-F	H	168 - 169.5 (dec.)

Referential Example 1

3-Amino-4-methylaminoquinoline A_{15}



A_{15}

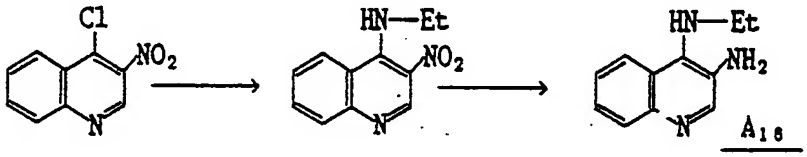
To a suspension of 2.0 g of 4-chloro-3-nitroquinoline in 20 ml of dry ethanol is added 15 ml of 30% methylamine in ethanol. The mixture is stirred at room temperature for 30 minutes and concentrated in vacuo. The residue is triturated with excess water. The resulting crystals are collected by filtration and washed repeatedly with water. The crystals are dried over phosphorus pentoxide in vacuo to afford 1.82 g - (93%) of 4-methylamino-3-nitroquinoline.

An analytical sample is recrystallized from ethyl acetate to give yellow crystals melting at 172 -173°C.
Anal. Calcd. (%) (for $C_{10}H_9N_3O_2$)
: C, 59.11; H, 4.46; N, 20.68.
Found (%) : C, 59.33; H, 4.59; N, 20.57.

A suspension of 1.7 g of 4-methylamino-3-nitroquinoline in 75 ml of ethanol is hydrogenated in the presence of 300 mg of 10% palladium on carbon at atmospheric pressure. After hydrogen absorption is complete, the catalyst is removed by filtration and the filtrate is concentrated in vacuo. The residue is purified by column chromatography on silica gel. Elution with chloroform -methanol (2:1 v/v) affords 600 mg (41%) of 3-amino-4-methylaminoquinoline A_{15} as an oil.
NMR (CD_3OD) : δ3.05(s,3H), 7.17-7.50(m,2H), 7.60-8.15(m,2H), 8.38 (s,1H).

Referential Example 2

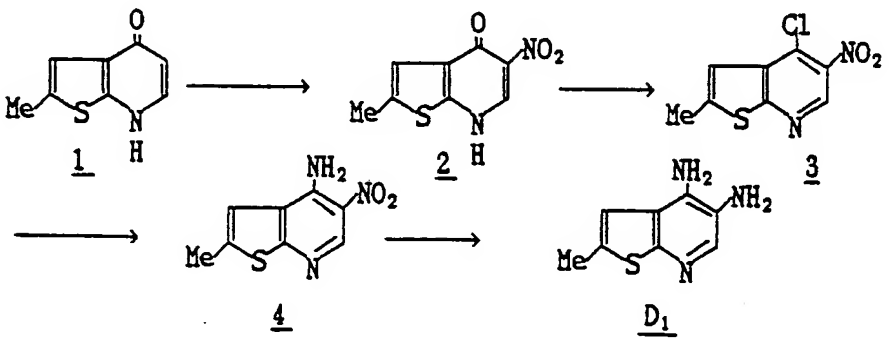
3-Amino-4-ethylaminoquinoline A_{16}



To a stirred suspension of 1.40 g of 4-chloro-3-nitroquinoline in 30 ml of dry ethanol is introduced excess amount of gaseous ethylamine at room temperature for 3 hours. Treatment of the reaction mixture as in Example 98 yielded 1.41 g (97%) of 4-ethylamino-3-nitroquinoline. Recrystallization from ethyl acetate -n-hexane affords yellow crystals melting at 151 -152°C.
Anal. Calcd. (%) (for $C_{11}H_{11}N_3O_2$)
: C, 60.82; H, 5.10; N, 19.34.
Found (%) : C, 60.93; H, 5.07; N, 19.27.

A suspension of 1.34 g of 4-ethylamino-3-nitroquinoline in 40 ml of ethanol is hydrogenated in the presence of 10% palladium on carbon according to the procedure of Referential Example 1, followed by purification to give 0.95 g (82%) of 3-amino-4-ethylaminoquinoline A_{16} as an oil.
NMR (CD_3OD): δ1.24(t,3H), 3.35(q,2H),7.33 -7.63(m,2H), 7.77 -8.03(m,2H), 8.30(s,1H).

Referential Example 3



(1) 5-Nitro-2-methylthieno[2,3-b]pyridin-4(7H)-one 2

To a solution of 1.65 g of 2-methylthieno[2,3-b]pyridin-4(7H)-one 1 in 45 ml of acetic is added dropwise a solution of 1.24 g of concentrated nitric acid (d = 1.38) in 5 ml of acetic acid at 110°C. The mixture is heated with stirring at the same temperature for 10 minutes and left on cooling. The resulting crystals are collected by filtration and washed with ethyl acetate to give 1.07 g (51%) of Compound 2 as pale yellow crystals melting at 280 -282°C(dec.).
Anal. Calcd. (%) (for $C_8H_6N2O_2S$)
: C, 45.71; H, 2.87; N, 13.32; S, 15.25.
Found (%) : C, 45.64; H, 3.42; N, 13.20; S, 15.20.

(2) 4-Chloro-5-nitro-2-methylthieno[2,3-b]pyridine 3

A mixture of 2.26 g of 5-nitro-2-methylthieno[2,3-b]pyridin-4(7H)-one 2 and 10 ml of phosphorus oxychloride is refluxed for 1 hour. The reaction mixture is concentrated to dryness in vacuo and the residue is taken up in the ethyl acetate. The organic phase is dried over magnesium sulfate and treated with activated charcoal. The mixture is filtered and the solvent is evaporated in vacuo. The crude product is recrystallized from ethyl acetate -n-hexane to give 1.90 g (68%) of Compound 3 as colorless melting at 96-98°C.
Anal. Calcd. (%) (for $C_8H_5N_2O_2SCl$)
C, 42.02; H, 2.20; N, 12.25; S, 14.02.
Found (%) : C, 41.92; H, 2.48; N, 12.16; S, 14.12.

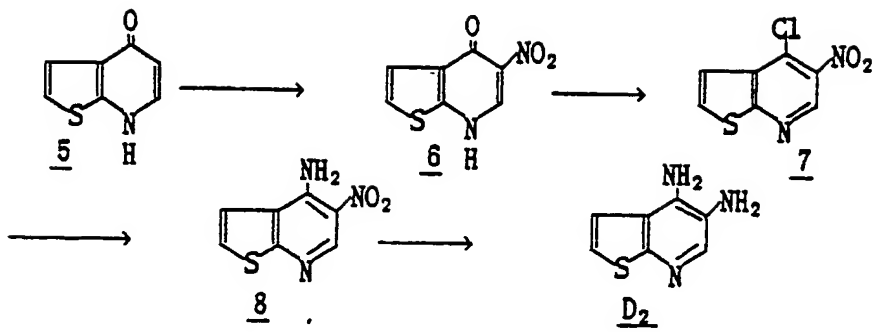
(3) 4-Amino-5-nitro-2-methylthieno[2,3-b]pyridine 4

To a stirred solution of 1.60 g of 4-chloro-5-nitro-2-methylthieno[2,3-b]pyridine 3 in 50 ml of 2-propanol is introduced excess amount of anhydrous ammonia at 55°C during 3 hours. The reaction mixture is concentrated in vacuo. The residue is washed with ether and suspended in 7 ml of 1N sodium hydroxide solution with stirring. The resulting crystals are collected by filtration and washed with water and a small amount of ethanol to yield 1.37 g (93%) of Compound 4 as orange crystals melting at 238 -240°C.
Anal. Calcd. (%) (for $C_8H_7N_3O_2S$)
: C, 45.92; H, 3,37; N, 20.08; S, 15.32.
Found (%) : C, 45.71; H, 3.40; N, 19.84; S, 15.44..

(4) 4,5-Diamino-2-methylthieno[2,3-b]pyridine D_1

A suspension of 1.25 g of 4-amino-5-nitro-2-methylthieno[2,3-b]pyridine is hydrogenated under atmospheric pressure at room temperature in the pressure of 360 mg of 10% palladium carbon for 2 hours. After removal of catalyst, the filtrate is concentrated and the residue is triturated with chloroform to give 866 mg (81%) of Compound D_1 as colorless crystals melting at 204 -209°C.
Anal. Calcd. (%) (for $C_8H_9N_3S$)
: C, 53.60; H, 5.06; N, 23.44; S, 17.88.
Found (%) : C, 53.56; H, 5.11; N, 23.24; S. 18.01.

Referential Example 4



(1) 5-Nitrothieno[2,3-b]pyridin-4(7H)-one 6

To a solution of 3.4 g of thieno[2,3-b]pyridin-4(7H)-one 5 in 105 ml of propionic acid is added 2.79 g of concentrated nitric acid (d = 1.38) at 100°C, and then the mixture is stirred at 130°C (bath temperature) for 1 hour. After cooling the reaction mixture, the resulting precipitate is collected by filtration and washed successively with water, methanol and acetone to afford 3.4 g (77%) of Compound 6 as pale yellow crystals melting at 288 - 291°C.

(2) 4-Chloro-5-nitrothieno[2,3-b]pyridine 7

A mixture of 3.4 g of 5-nitrothieno[2,3-b]pyridin-4(7H)-one6 and 34 ml of phosphorus oxychloride is heated at 115°C (bath temperature) for 1 hour and evaporated to dryness in vacuo. The residue is taken up in chloroform and washed with water. The organic phase is dried over magnesium sulfate and concentrated in vacuo. The residue is purified by column chromatography on silica gel. Elution with dichloromethane - ether (50:1 v/v) affords 3.51 g (94%) of Compound 7 as crystals melting at 110 -113°C.

(3) 4-Amino-5-nitrothieno[2,3-b]pyridine 8

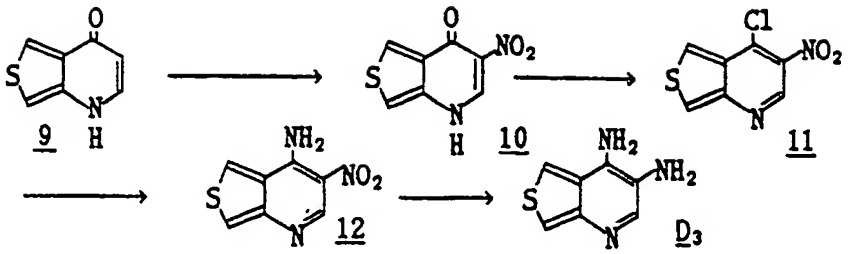
To a stirred suspension of 3.35 g of 4-chloro-5-nitrothieno[2,3-b]pyridine 7 in 160 ml of 2-propanol is introduced excess amount of anhydrous ammonia at 45 -50°C during 4 hours. After removal of the solvent, the residue is suspended in water. The solid is washed with water and cold ether, affording 2.65 g (87%) of Compound 8 as crystals. Recrystallization from methanol -ether gives a pure sample melting at 227 - 228.5°C.

(4) 4,5-Diaminothieno[2,3-b]pyridine D_2

A mixture of 2.57 g of 4-amino-5-nitrothieno[2,3-b]pyridine 8 and 11.1 g of stannous chloride in 240 ml of ethanol is stirred at 75°C for 3 hours. The reaction mixture is treated with activated charcoal and filtered. After concentration of the filtrate, the residue is taken up in ethyl acetate and suspended in 185 ml of 5% aqueous sodium bicarbonate. The organic layer is extracted with dilute hydrochloric acid. The aqueous layer is treated with activated charcoal and filtered. The filtrate is basified to pH = 10 with 10% sodium hydroxide and extracted with ethyl acetate. The extract is dried over magnesium sulfate and evaporated in vacuo. The residue is recrystallized from ethyl acetate -ethe. to afford 1.65 g (76%) of Compound D_2 as pale yellow crystals melting at 159 -160.5°C.

Anal. Calcd. (%) (for $C_7H_7N_3S \cdot 1/8H_2$)
: C, 50.20; H, 4.36; N, 25.09.
Found (%) : C, 50.54; H, 4.24; N, 24.95.

Referential Example 5



(1) 3-Nitrothieno[3,4-b]pyridin-4(1H)-one 10

To a suspension of 4.00 g of thieno[3,4-b]pyridin-4(1H)-one 9 in 120 ml of acetic acid is added 3.00 g of nitric acid (d = 1.38). The reaction mixture is stirred at 70°C for 3 minutes and cooled to room temperature. The resulting crystals are collected by filtration, and then washed with water and methanol - ether , affording 2.51 g (48%) of Compound 10. An analytical sample is recrystallized from dimethylsulfoxide -methanol to give yellow crystals melting at 329 -332°C.

Anal. Calcd. (%) (for $C_7H_4N_2O_3S$)
: C, 42.85; H, 2.05; N, 14.27.
Found (%) : C, 42.75; H, 2.30; N, 14.13.

(2) 4-Chloro-3-nitrothieno[3,4-b]pyridine 11

A mixture of 3.00 g of 3-nitrothieno[3,4-b]pyridin-4(1H)-one 10 and 9 ml of phosphorous oxychloride is stirred at 105°C (bath temperature) for 1 hour and evaporated to dryness in vacuo. The residue is taken up in chloroform and washed with aqueous ammonia and water. The organic phase is dried over magnesium sulfate and evaporated. The residue is purified by column chromatography on silica gel. Elution with dichloromethane -ether (50:1 v/v) affords 2.02 g (60%) of Compound 11. Recrystallization from ether - petroleum ether affords colorless crystals melting at 139 -140°C.

Anal. Calcd. (%) (for $C_7H_3N_2O_2ClS \cdot 1/8H_2O$)
: C, 38.77, H, 1.51; N, 12.92.
Found (%) : C, 38.60; H, 1.55; N, 12.79.

(3) 4-Amino-3-nitrothieno[3,4-b]pyridine 12

To a stirred suspension of 1.25 g of 4-chloro-3-nitrothieno[3,4-b]pyridine 11 in 37 ml of 2-propanol is introduced anhydrous ammonia at room temperature during 3 hours. The mixture is concentrated in vacuo and the residue is suspended in water with stirring. The crystals are collected by filtration, washed with water and dried to give 1.09 g (96%) of Compound 12. An analytical sample is recrystallized from chloroform -methanol, giving yellow crystals melting at 307 -309°C.

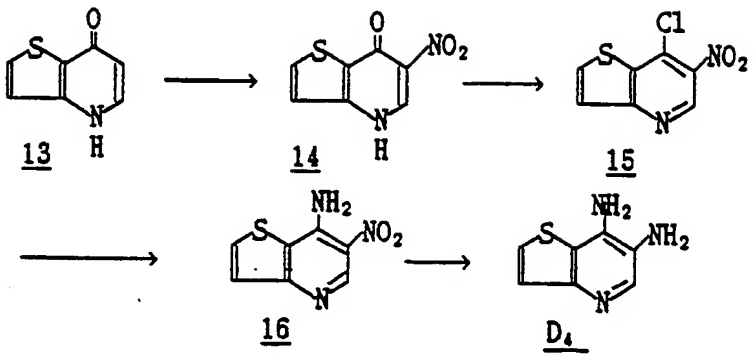
Anal. Calcd. (%) (for $C_7H_5N_3O_2S$)
: C, 43.07; H, 2.58; N, 21.52.
Found (%) : C, 42.93; H, 2.69; N, 21.36.

(4) 3,4-Diamino[3,4-b]pyridine D_3

A mixture of 620 mg of 4-amino-3-nitrothieno[3,4-b]pyridine and 3.59 g of stannous chloride dihydrate in 50 ml of ethanol is stirred at 70°C for 1 hour. After evaporation of the solvent in vacuo, the residue is partitioned between ethyl acetate and aqueous sodium bicarbonate. The resulting solid is filtered off and washed with ethyl acetate. The combined extracts are dried and evaporated in vacuo. The residue is purified by column chromatography on neutral alumina. Elution with chloroform -methanol (20:1 v/v) affords 490 mg (93%) of Compound D_3, which is recrystallized from ether -methanol to afford colorless crystals melting at 140 -144°C.

Anal. Calcd. (%) ($C_7H_7N_3S \cdot 2/3H_2O$)
: C, 47.44; H, 4.74; N, 23.71.
Found (%) : C, 47.68; H, 4.85; N, 23.24.

Referential Example 6



(1) 6-Nitrothieno[3,2-b]pyridin-7(4H)-one 14

To a solution of 3.1 g of thieno[3,2-b]pyridin-7(4H)-one 13 in 90 ml of propionic acid is added 1.5 ml of fuming nitric acid at 110°C with stirring and the mixture is refluxed for 1 hour. The cooled mixture is diluted with 50 ml of ether and the resulting crystals are collected by filtration, washed with water and ether - methanol, and dried to give 3.13 g (78%) of Compound 14. Recrystallization from dimethyl sulfoxide - methanol affords colorless crystals melting at 328 -331°C (dec.).
Anal. Calcd. (%) (for $C_7H_4N_2O_3S$)
: C, 42.85; H, 2.05; N, 14.27.
Found (%) : C. 42.88; H, 2.17; N, 14.21.

(2) 7-Chloro-6-nitrothieno[3,2-b]pyridin-7(4H)-one 15

A mixture of 2.7 g of 6-nitrothieno[3,2-b]pyridin-7(4H)-one 14 and 30 ml of phosphorous oxychloride is stirred at 115°C for 1 hour. The reaction mixture is evaporated to dryness in vacuo. The residue is taken up in dichloromethane, washed successivly with aqueous ammonia and water, and then dried over magnesium sulfate. The solvent is removed in vacuo and the crude crystals are purified by column chromatography on silica gel. Elution with dichloromethane -ether (50:1 v/v) affords 2.64 g (90%) of Compound 15. Recrystallization from ether gives colorless crystals melting at 124 -125.5°C.
Anal. Calcd. (%) (for $C_7H_3N_2O_2ClS$)
: C, 39.17; H, 1.40; N, 13.05.
Found (%) : C, 38.96; H, 1.70; N, 12.92.

(3) 7-Amino-6-nitrothieno[3,2-b]pyridine 16

To a suspension of 2.55 g of 7-chloro-6-nitrothieno[3,2-b]pyridine 15 in 130 ml of 2-propanol is introduced excess anhydrous ammonia at 45°C (bath temperature) during 4 hours and the mixture is evaporated in vacuo. The residue is suspended in water, collected by filtration, and then washed with water and ether to give 2.30 g (99%) of Compound 16. An analytical sample is recrystallized from chloroform methanol, affording yellow crystals melting at 266 -268.5°C.

Anal. Calcd. (%) (for $C_7H_5N_3O_2S$)
: C, 43.07; H, 2.58; N, 21.52.
Found (%) : C, 43.02; H, 2.76; N, 21.46.

(4) 6,7-Diaminothieno[3,2-b]pyridine D_4

A mixture of 2.3 g of 7-amino-6-nitrothieno[3,2-b]pyridine 16 and 12.5 g of stannous chloride dihydrate in 160 ml of ethanol is heated with stirring at 70°C for 3 hours. The mixture is evaporated in vacuoand the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate. The resulting solid is filtered off and washed with ethyl acetate. The combined extracts are dried and evaporated in vacuo. The residue is purified by column chromatography on silica gel. Elution with chloroform -methanol (10:1 v/v) affords 1.91 g (97%) of Compound D_4 which is recrystallized from methanol -ether to give colorless melting at 157-159°C.
Anal. Calcd. (%) (for $C_7H_7N_3S \cdot 1/4H_2O$)
: C, 49.54; H, 4.45; N, 24.76.
Found (%) : C, 49.79; H, 4.35; N, 24.43.

Preparation

2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]quinoline	..... 10 mg
Wheat starch	..... 48 mg
Magnesium stearate	..... 2 mg

The above components are mixed each other to prepare a capsule.

Effect of the Invention

The compounds of the present invention show high affinity to a benzodiazepine receptor. The drugs bound to this receptor are classified as three groups according to the difference of the efficacy. Thus, agonists can be utilized as anxiolytics or anticonvulsants, antagonists can be agents for treating benzodiazepine intoxication and accidental supernumerary uptake, and inverse agonists are expected as psychostimulants.

Experiments for assessing biological activities of the compounds of the present invention are shown below; the number of the test compound nearly corresponds to the number used in Examples and Tables respectively.

Experiment 1

Binding test to benzodiazepine receptor

This test was carried out in the modified method of Möhler et al. Science, 198, 849-851 (1977).

Receptor preparation was provided from the cerebral cortex of Wistar rats (male, 11 to 13 weeks age). Inhibitory action of the test compound on the specific binding of tritium labeled diazepam to the receptor was evaluated as follows. 2nM tritium labeled diazepam and an aqueous solution of the test compound at 5 or 6 concentrations were incubated with the receptor preparation at 0°C for 6 minutes. The 50% inhibitory concentration (IC_{50}) was measured by the concentration-response curve.

The inhibitory constant (Ki) was calculated according to the following equation, in which Kd is the dissociation constant of the tritium labeled diazepam and L is the concentration of the labeled ligand.

$$Ki = \frac{IC_{50}}{1 + L/Kd}$$

Compound No.	Ki (nM)	Compound No.	Ki (nM)
C_2	0.97	C_{58}	0.525
C_3	15.8	C_{59}	1.23
C_{13}	8.73	C_{60}	0.495
C_{20}	27.7	C_{61}	0.661
C_{21}	1.80	C_{67}	2.07
C_{27}	1.88	C_{68}	1.19
C_{35}	19.5	C_{70}	5.40
C_{36}	15.6	C_{71}	4.57
C_{45}	0.582	F_2	31.8
C_{46}	0.97	F_7	725
C_{48}	0.907	K_6	10.1
C_{49}	0.237		

Experiment 2

Antagonism of Pentyleneterazole-Induced Convulsion

Agonistic activity was evaluated in this test. Groups of 8-16 male mice were challenged with a dose of 125 mg/kg, s.c. of pentylenetetrazole immediately after intravenous injection of the test compound. The dose required to prevent tonic convulsion and death in 50% of the animal during a 2-h observation period was calculated by the probit method.

Compound No.	ED_{50} (mg/Kg)
C_2	15.97
C_3	2.31
C_{13}	4.61
C_{20}	3.90
C_{21}	2.05
C_{27}	1.41
C_{38}	8.52
C_{48}	0.71
C_{48}	1.20
C_{48}	0.59
C_{49}	0.32
C_{89}	3.01
C_{91}	0.74

Experiment 3

Potentiation of Pentylenetetrazole-Induced Convulsion

Inverse agonist activity was evaluated in this test. Groups of 8-16 mice were challenged with a dose of 90 mg/kg. s.c. of plentylenepetrazole (a subconvulsive dose) immidiately after intraveonous injection of the test compound. The dose required to produce tonic convulsion and death in 50% of the animal during a 2-h observation period was calculated by the probit method.

Compound No.	ED_{50} (mg/Kg)
C_{36}	1.76
C_{58}	1.65
C_{71}	4.18
F_2	0.13
K_6	0.54
F_7	0.50

Experiment 4

Traction test

The modified method of Courvoisier et al. (in "Psychotropic Drugs", ed. by S. Garattini & R. Ducrot. p 373. Elsevier Publishing Co., Amsterdam 1957) was employed. Groups of 10 mice were made to hang onto a horizontal metal wire (diameter : 1 mm) by grasping and holding with their forepaws 30 minutes after oral administration of the test compound, and the number of mice gripping the wire with hindpaws within 10 sec was counted. The ED_{50} was calculated by the probit method.

Experiment 5

Anticonflict test

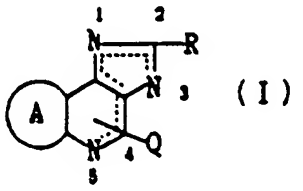
The modified method of Geller and Seifter (Psychopharmacol, 1, 482, 1960) was employed. Groups of 5 or more male Wistar rats with well-established conflict behavior were used. A dose was determined as positive when the number of electric shocks (punishment) exceeded more than 12 during a 1 hour observation period starting 30 minutes after oral administration of the test compound. The ED_{50} was calculated by the probit method.

Compound No.	Anti-conflict activity ED_{50}(mg/kg)	Traction Test ED_{50}(mg/kg)
C_{46}	2.68	〉200
C_{48}	1.80	〉200
C_{49}	1.19	〉200
Diazepam	1.05	5.06

The pharmacological activities described above suggest that the dissociation of anxiolytic action and muscle relaxation action, both being specific to drugs of benzodiazepine type, was achieved. Thus, the compound of the present invention can be an anxiolytic drug not accompanying with a side effect such as dizziness.

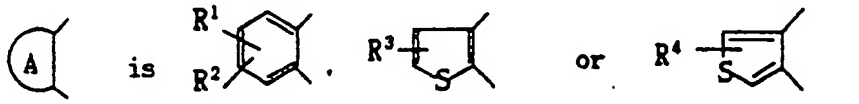
Claims

1. A compound of the formula:



(I)

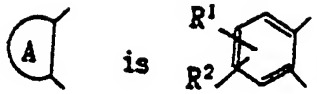
wherein R is phenyl optionally substituted by one or two of trifluoromethyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 alkylthio, nitro, amino, C_1-C_5 alkanoylamino and C_1-C_5 alkoxycarbonyl, or a 5-or 6-membered heterocyclic group optionally substituted by one or two of halogen, C_1-C_5 alkyl and C_1-C_5 alkoxy;
Q is hydrogen, C_1-C_5 alkyl, C_{1-10} acyl, C_1-C_5 alkylsulfonyl or C_6-C_{10} arylsulfonyl,



;

R^1, R^2, R^3 and R^4 are each independently hydrogen, halogen, C_1-C_5 akyl, C_1-C_5 alkoxy or C_1-C_5 haloalkyl;
Q is present on the nitrogen atom at the 1, 3 or 5-position, and the dotted line indicates the presence of three double bonds at the position of 2, 3; 3a, 3b; 4, 5/1, 3b; 2, 3; 3a, 4/ or 1, 2; 3a, 3b; 4, 5

2. A compound as claimed in Claim 1, wherein

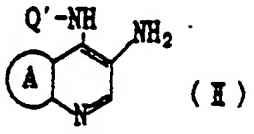


3. A compound as claimed in Claim 1 or Claim 2, wherein R is a 5-membered heterocyclic group optionally substituted by one or two of halogen, C_1-C_5 alkyl and C_1-C_5 alkoxy. e.g. 2-thienyl or 3-methyl-5-isoxazolyl.

4. 7-Chloro-2-(2-thienyl)-1H-imidazo[4,5-c]quino line;
2-(3-methylisoxazol-5-yl)-1H-imidazo[4,5-c]qu inoline;
7-fluoro-2-(3-methylisoxazol-5-yl)-1H-imidazo [4,5-c]quinoline; or
8-fluoro-2-(3-methylisoxazol-5-yl)-1H-imidazo [4,5-c]quinoline.

5. A compound as claimed in any one of claims 1 to 4 which is as an acid addition salt thereof.

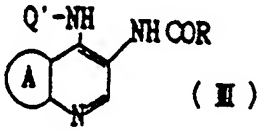
6. A process for preparing a compound as claimed in Claim 1, which comprises reacting a compound of the formula:



(II)

wherein Q' is hydrogen or C_1-C_5 alkyl and

is as defined in Claim 1. with an acylating agent to give a compound of the formula:



(III)

wherein

, Q' and R each is as defined in Claim 1 and cyclizing the compound (III), and when Q is hydrogen, applying the cyclized product to alkylation, acylation or sulfonylation, if necessary.

7. A pharmaceutical or veterinary formulation comprising a compound as claimed in any one of claims 1 to 5 formulated for pharmaceutical or veterinary use, respectively, optionally in unit dosage form and/or further comprising a pharmaceutically or veterinarily acceptable carrier, diluent or excipient.

8. A compound as claimed in any one of claims 1 to 5 or a compound which has been prepared by a process as claimed in claim 6, for use in the treatment of disease.

9. The use of a compound as claimed in any one of claims 1 to 5 or a compound which has been prepared by a process as claimed in claim 6, for the manufacture of a medicament for the treatment of anxiety or depression.

10. A method of making a pharmaceutical or veterinary formulation which comprises mixing a compound as claimed in any one of claims 1 to 5 or a compound which has been prepared by a process as claimed in claim 6, with a pharmaceutically or veterinarily acceptable carrier, diluent or excipient.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 86 30 8087

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	EP-A-0 145 340 (RIKER LABORATORIES, INC.) * claims 1, 15, 16 *	1,2,6, 8	C 07 D 471/04 C 07 D 495/14 A 61 K 31/47 // (C 07 D 471/04 C 07 D 235:00 C 07 D 221:00) (C 07 D 495/04 C 07 D 333:00 C 07 D 235:00 C 07 D 221:00)
A	CHEMICAL ABSTRACTS, vol. 94, no. 7, 16th February 1981, page 570, column 2, abstract no. 47216f, Columbus, Ohio, US; M.M. ABBASI et al.: "Base induced cyclization of some quinolines. Formation of fused nitrogen heterocyclic ring system", & MONATSH. CHEM. 1980, 111(4), 963-969 (Cat. D,A)	1,2,6	
P,A	DD-A- 238 235 (CIBA-GEIGY AG) * page 6, formulae 1A, 1B; page 9, formula III; page 10, formula VI; page 11, formulae VIB, VIC *	1,2	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)
C 07 D 471/00 C 07 D 495/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	13-01-1987	HASS C V F

CATEGORY OF CITED DOCUMENTS

- X : particularly relevant if taken alone
- Y : particularly relevant if combined with another document of the same category
- A : technological background
- O : non-written disclosure
- P : intermediate document
- T : theory or principle underlying the invention
- E : earlier patent document, but published on, or after the filing date
- D : document cited in the application
- L : document cited for other reasons
- & : member of the same patent family, corresponding document

EPO Form 1503 03.82